PYELONEPHRITIS

Observations on the relation between various diagnostic procedures

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IT is usually difficult to be certain about the presence or extent of an upper urinary infection. Kleeman et al. (1960), reviewing 629 cases of pyelonephritis diagnosed at necropsy, found that the diagnosis had been made clinically in only 17%. We here describe our findings during an investigation of Pears and Houghton's (1959) pyrogen test for infection in the urinary tract. The relation between the clinical history, the presence of organisms in the urine, the rate of urinary white-cell excretion before and after the administration of a pyrogen, radiological abnormalities, and the renal-biopsy findings in acute and chronic pyelonephritis are presented. Some observations on the urinary white-cell excretion-rate before and after the administration of a pyrogen in glomerular nephritis, "essential" hypertension, and asymptomatic urethritis are also described.

Methods

Renal biopsy, intravenous pyelography, and aortograms were performed by routine techniques. Urine for culture and white-cell excretion-rate was obtained from the men by natural voiding after thoroughly cleaning the penile meatus. Urine was taken from the women by catheterisation; after removing the catheter tetracycline or sulphadimidine was given prophylactically for twenty-four hours. The urine was collected with a catheter so that we could compare our results with those of Pears and Houghton (1959).

The pyrogen test was performed in the following way. Urine for control observations was collected from 8 A.M. to 12 noon. At noon 'Pyrexal' (Wander †) 0·07 μg. per kg. was given intravenously, and the urine was collected at 1 and 2 P.M. All three specimens of urine were collected into sterile containers, they were plated for culture on McConkey's medium by 2.30 P.M., and their content of white cells was estimated by 4 P.M. The inoculated plates were examined after overnight incubation, and any colonies were identified in the usual way.

The normal white-cell excretion-rate is usually below 200,000 per hr., though a rate of between 200,000 and 400,000 per hr. was found in 2 of 60 normal subjects (de Wardener and Chambers, unpublished observations). The results of an intravenous injection of pyrogen in 10 normal subjects are shown in fig. 1, where it can be seen that the white-cell excretion either rose or fell but never changed to more than 200,000 per hr.

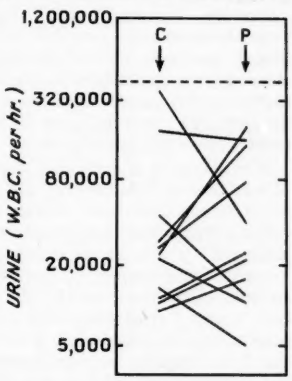

Fig. 1—Normal subjects: urinary white-cell excretion-rate (C) before and (P) after administration of pyrogen.
The broken horizontal line indicates a rate of 400,000 per hr.

Acute Pyelonephritis

An acute upper urinary infection may affect a previously normal kidney, or it may be superimposed upon an underlying persistent pyelonephritis or some other cause of renal structural deformity (e.g., polycystic kidney). The findings are described in 15 patients who had recently (table I) had an upper urinary infection, but in whom there was no previous history of urinary infection nor any evidence of an underlying previous pyelonephritis or other chronic renal abnormality. Each of these patients had had loin pain and tenderness, fever, frequency, and dysuria, and large numbers of organisms and white cells were found in the urine during the acute phase. All patients had had some antibiotic therapy before admission to

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† Purified lipopolysaccharide obtained from *Salmonella abortus equi*.

TABLE I—ACUTE PYELONEPHRITIS

Case no.	Sex	Age (yr.)	Interval since recent infection (days)	Biopsy findings	I.V.P.	White-cell excretion-rate per hr.		Culture at time of cell-count	Proteinuria	Creatinine-clearance (ml. per min.)	Maximum specific gravity	Blood-pressure (mm. Hg)
						Control	After pyrogen					
1	F	43	5	Acute pyelonephritis	Normal†	14,615,000	108,609,000	+	Nil	49	1007	130/90
2*	F	21	70	" "	Normal	43,000	40,200	+	"	99	1028	125/70
3*	F	22	56	" "	Slight clubbing of right calyces; compatible with recent pregnancy	738,000	5,640,000	+	"	45	1020	125/75
4*	F	31	10	" "		—	—	+	+	97	—	120/70
5	F	57	7	" "	Attenuated elongated left upper calyx, and enlarged upper pole; suggestive of tumour	8,000,000	—	+	Nil	50	—	100/60
6	F	30	21	Normal	Normal	43,000	183,000	Sterile	"	112	1024	120/80
7	F	31	60	"	"	198,000	2,940,000	"	"	78	1028	110/70
8*	F	21	90	"	"	53,000	8,000,000	"	+	75	—	130/80
9	F	58	4	"	Rotated right kidney; dilated pelvis	1,000,000	2,360,000	"	Nil	48	1022	170/105
10	M	29	14	"	Normal	47,250	81,000	"	"	113	1020	150/85
11	F	31	35	"	"	709,000	241,000	"	"	69	1020	130/80
12	F	27	14	Not done	"	80,000	9,000	"	"	90	—	110/70
13	F	24	14	" "	"	24,625	141,000	"	"	82	—	130/80
14	F	22	14	" "	"	400,000	2,285,000	+	Trace	—	—	110/60
15	M	39	7	" "	Normal†	1,102,500	1,420,000	Sterile	Nil	71	—	110/70

* = pregnant. † = no abnormality seen but opacification only moderate.

hospital, and most were either symptomless or only had residual loin tenderness or mild dysuria on admission.

Renal Biopsy

Adequate renal biopsies were obtained from 10 patients, and a nephrectomy specimen was available from another patient. 5 showed evidence of pyelonephritis. 3 of these 5 were from the 4 women in the group who had pyelonephritis during pregnancy; the biopsies were performed during the puerperium ten days, eight weeks, and ten weeks after the onset of acute symptoms. In cases 1 and 3, two renal biopsies were taken from the same kidney on the same day; in both patients one biopsy specimen showed normal cortex whereas the other showed gross pyelonephritis (fig. 2). The renal biopsies from cases 2 and 4 showed focal involvement of the kidney. The nephrectomy specimen (case 5) showed widespread involvement with some normal areas.

The diagnosis of acute pyelonephritis was based on focal or diffuse areas of inflammatory-cell infiltration, with an increase of interstitial tissue and tubular degeneration. In all 5 cases polymorphonuclear leucocytes were identified among the inflammatory cells in the interstitial tissue, or in the tubular lumens. Lymphocytes, occasional plasma-cells, macrophages, and eosinophils accounted for the other inflammatory cells. In cases 1 and 5 renal tissue was taken within seven days of an acute attack and polymorphs predominated, whereas in cases 2 and 3 the biopsies were performed after intervals of fifty-six and seventy days and only occasional polymorphs were seen. The tubular epithelium in the affected areas was often atrophic, and the cell cytoplasm was exfoliated. It was often almost impossible to recognise the tubules among the dense inflammatory cells; many tubules contained amorphous or cellular casts infiltrated by polymorphs, and polymorphs were occasionally present in the cytoplasm of the tubular cells. In some sections stained by the periodic-acid (Schiff) technique focal ruptures of the tubular basement membrane could be seen. In case 5, in addition to these features, necrotising papillitis was apparent in one papilla. In all these cases the glomeruli remained well preserved apart from occasional slight periglomerular fibrosis.

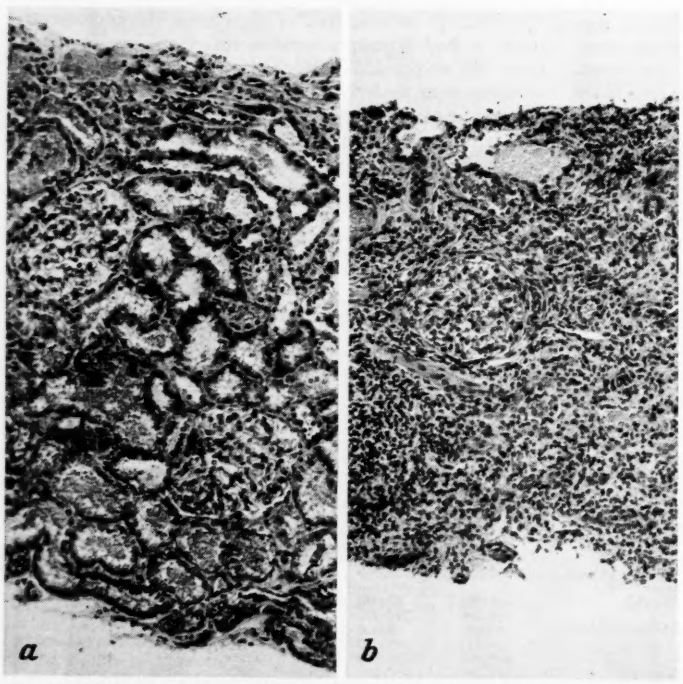

Fig. 2—Sections of two renal biopsies (case 3) taken from the same kidney at the same time, showing (*a*) normal renal cortex, and (*b*) gross acute pyelonephritis.

I.V.P.

All 15 patients had an intravenous pyelogram (I.V.P.); none had an aortogram. Only cases 5 and 9 showed an unequivocal abnormality. In case 5 this consisted of compression and elongation of the upper calyx of the left kidney, together with uniform enlargement of the upper pole. Because these changes were considered to be due to a neoplasm, nephrectomy was performed. Some of the macroscopic and microscopic appearances of this kidney have been described in the preceding paragraph. There was intense acute pyelonephritis involving the whole kidney, being particularly severe in the upper pole. The radiological appearances resulted from pericalyceal œdema associated with necrotising papillitis. Case 9 showed a dilated pelvis in a rotated kidney.

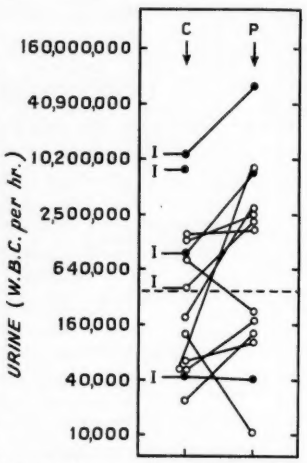

Fig. 3—Acute pyelonephritis: urinary white-cell excretion-rate (C) before and (P) after administration of pyrogen.

I=patient with infected urine. The broken horizontal line indicates a rate of 400,000 per hr. ●=histological evidence of acute pyelonephritis. O=no biopsy.

2 of the 4 patients with biopsy evidence of acute pyelonephritis had a normal I.V.P. (cases 1 and 2), but the opacification in case 1 was only moderate. Case 2 had been delivered a month before the investigations were performed. Cases 3 and 4 had been delivered twelve days and a month before; the I.V.P. in both showed slight clubbing of the calyces of the right kidney, the appearances being compatible with a recent pregnancy.

Proteinuria

Only 3 patients had proteinuria. In the other 12 the urine was free of protein, though 4 of these showed biopsy evidence of acute pyelonephritis in the cortex, and the urine was infected.

Urine-cultures

The urine was infected in 6 patients, and 4 of these had had some form of antibiotic therapy within the preceding month. The other 2 had been treated four and eight weeks before admission.

Control Urinary White-cell Excretion-rate

The white-cell excretion-rate was greater than normal (i.e., above 400,000 per hr.) in 6 of the 14 patients in whom it was measured; in 3 of the 6 the urine was sterile. Conversely, the excretion-rate was normal in 1 patient with infected urine (fig. 3).

Pyrogen Test

After the injection of pyrogen the rate of white-cell excretion increased by 100% or more, and was greater than 400,000 per hr. in 6 of the 13 patients in whom the test was performed (fig. 3). In 2 of these 6 the control urinary white-cell excretion-rate was normal, and the urine was sterile. In 1 patient with a raised control white-cell excretion-rate the white-cell excretion fell after pyrogen was given.

Arterial Pressure and Glomerular Filtration-rate

The diastolic blood-pressure was 85 mm. Hg or lower in 13 of the 15 patients. In the

other 2 it was 90 and 105 mm. The glomerular filtration-rate as measured by creatinine-clearance was 69–113 ml. per min. in 10 of the 14 patients in whom it was measured. In the 5 patients with histological evidence of pyelonephritis it was 45, 49, 50, 97, and 99 ml. per min.

Chronic Pyelonephritis

The clinical manifestations of chronic pyelonephritis vary from symptomless proteinuria to advanced renal failure with hypertensive cardiac failure, and there may be no clear history of urinary infections. In contrast to acute pyelonephritis, therefore, it is more difficult to delineate a group of patients in whom to study the various methods which are used to diagnose chronic pyelonephritis. To obtain such a group a diagnosis of chronic pyelonephritis was considered established if either (1) a renal biopsy showed evidence of chronic pyelonephritis, or (2) a history of recurrent urinary infection was elicited and the I.V.P. was abnormal. The 26 patients who satisfied these criteria are listed in table II, with the results of the various investigations performed.

TABLE II—CHRONIC PYELONEPHRITIS

Case no.	Sex	Age (yr.)	Biopsy findings	I.V.P.	Aortogram	White-cell excretion-rate per hr.		Culture at time of cell-count	Treatment within a month	Proteinuria	Creatinine-clearance (ml. per min.)	Maximum specific gravity	Blood-pressure (mm. Hg)	History of urinary infection
						Control	After pyrogen							
16	F	35	Definite chronic pyelonephritis	Normal	Doubtful cortical scarring	3,200,000	20,400,000	+	None	+	60	1012	250/160	−
17	F	40	„ „	„	..	56,000	1,539,000	? contaminated	„	+	42	..	150/100	−
18	F	59	„ „	No opacification	..	225,000	4,800,000	? contaminated	„	+	54	..	230/120	−
19	F	41	„ „	Normal	..	891,000	20,698,000	+	„	Trace	49	1020	290/160	+
20	F	24	„ „	Right deformed calyx and cortical thinning	Cortical scarring; right kidney 1·5 cm. smaller than left	449,000	1,316,000	+	„	+	87	..	160/90	+
21	M	24	„ „	Left calculus	..	2,098,190	3,780,000	Sterile	„	+	47	1012	250/140	−
22	F	29	„ „	Normal	Doubtful cortical scarring	34,375	108,000	? contaminated	Yes	Nil	77	1030	140/90	+
23	M	38	„ „	„	..	207,000	228,000	Sterile	None	+	28	1014	125/95	−
24	M	49	„ „	No opacification	..	166,000	386,000	„	„	+	15	1008	200/130	−
25	F	31	Probable chronic pyelonephritis with glomerular nephritis	Normal	Fœtal lobulation	449,000	1,296,000	„	„	+++	73	1016	150/110	+
26	F	32	Probable chronic pyelonephritis	Deformed calyces; cortical thinning	..	544,000	1,000,000	„	Yes	+	66	1013	140/90	+
27	M	58	„ „	Normal	..	1,305,000	1,890,000	„	None	++	82	1022	160/80	−
28	M	28	Normal	Right calculus	..	745,500	2,384,000	+	„	Nil	90	..	200/120	+
29	M	60	Not performed	Left staghorn calculus	..	927,000,000	304,000,000	+	Yes	Trace	36	..	140/90	+
30	F	36	„ „	Right calculus and hydronephrosis; left bifid pelvis	..	7,632,500	35,750,000	+	„	Nil	79	1022	150/85	+
31	M	52	„ „	Right calculus and clubbing	..	997,000	1,790,000	Sterile	„	„	80	1016	150/110	+
32	F	38	Normal	Right clubbing and hydronephrosis	Stenosed left renal artery	762,000	72,000,000	„	„	Trace	79	1020	190/125	+
33	F	25	Not performed	Right clubbing	..	48,000	280,000	„	„	Nil	..	..	120/70	+
34	M	17	„ „	Right and left hydronephrosis, hydroureter, and cortical thinning	..	162,000	437,000	„	„	+	43	1008	120/80	+
35	F	22	„ „	Left and right hydronephrosis	..	101,000	53,000	„	„	Nil	80	1020	120/75	+
36	F	45	„ „	Right clubbing	..	400,000	1,000,000	+	None	„	57	1016	130/80	+
37	F	31	„ „	Right cortical thinning and calyceal deformity	..	1,380,000	9,085,000	+	„	+	50	1027	230/135	+
38	F	31	Normal	Right double pelvis and cortical thinning	..	105,000	33,000	Sterile	Yes	Nil	70	1020	100/70	+
39	F	33	Not performed	Right double pelvis and ureter	..	81,000	400,000	„	None	Trace	53	..	160/120	+
40	F	20	Normal	Left double pelvis*	..	220,000	3,225,600	+	„	+	105	1026	180/115	+
41	F	36	Not performed	Right double pelvis and ureter	..	2,198,000	12,698,000	Sterile	Yes	Nil	76	1024	120/80	+

* There was also a rounded defect in the right upper major calyx, with a sharp margin suggestive of arterial pressure.

Renal Biopsies

Renal biopsies were taken from 16 patients in this group. Four of the biopsies showed no structural abnormality; this does not, of course, exclude a diagnosis of pyelonephritis in view of the focal nature of the disease. Among those patients with structural abnormalities case 25 also showed changes suggestive of glomerular nephritis. 12 patients had patchy or diffuse chronic inflammatory-cell infiltration in the renal cortex, with an increase of interstitial tissue and some tubular degeneration in the affected areas. In addition, there was always some glomerular tuft fibrosis, often with pronounced periglomerular fibrosis. The inflammatory cells in the interstitial tissue in these cases were similar to those in the acute group, except that polymorphs were only identified with certainty in case 16. In 9 cases the inflammatory-cell infiltration and the distended tubules containing eosinophilic casts (thyroid areas) enabled pyelonephritis to be diagnosed with reasonable certainty. The remaining 3 cases, called " probable pyelonephritis ", showed smaller foci of chronic inflammatory cells associated with fibrosis of glomeruli but without the typical

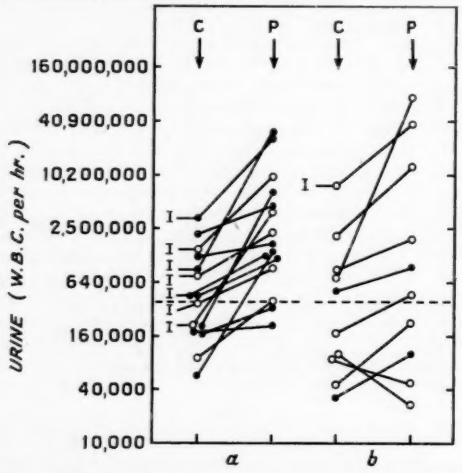

Fig. 4—Chronic pyelonephritis: urinary white-cell excretion-rate (C) before and (P) after administration of pyrogen in (*a*) 15 patients who had not been treated recently and (*b*) 10 patients who had had a course of antibiotics within the preceding month.

I=patient with infected urine. The broken horizontal line indicates a rate of 400,000 per hr. ●=histological evidence of pyelonephritis. O=no biopsy.

thyroid-like tubules. Only 5 of these 12 patients with histological evidence of pyelonephritis gave a history of previous renal infection.

I.V.P.

I.V.P.s were performed in all 26 patients, and aortograms in 5. No shadow was obtained on I.V.P. in 2. In the others the appearances were normal in 7 and abnormal in 17. The I.V.P. was technically satisfactory in 10 patients with biopsy evidence of chronic pyelonephritis; and in 7 the I.V.P. appeared normal, though in 2 of these aortography suggested cortical scarring. I.V.P. abnormalities included cortical thinning, calyceal deformities, and calculi. In 3 the only abnormality was a double pelvis.

Proteinuria

17 of the 26 patients had proteinuria. 11 of those with renal-biopsy evidence of chronic pyelonephritis had proteinuria, whereas it was present in only 9 of the 17 with an abnormal I.V.P. The only patient with extensive proteinuria (8–12 g. per day) had histological evidence of chronic glomerular nephritis in addition to pyelonephritis. In 3 of the patients without proteinuria the urine was infected, and the urinary white-cell excretion-rate was high, rising briskly after the administration of a pyrogen.

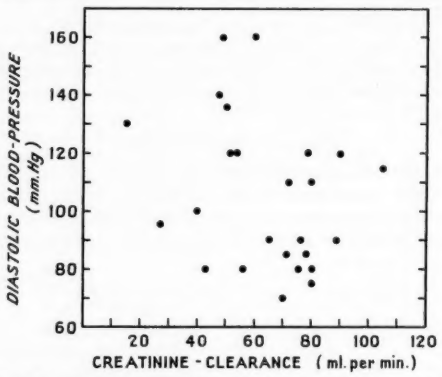

Fig. 5—Chronic pyelonephritis: the relation between diastolic arterial pressure and creatinine-clearance.

Urine-culture and White-cell Excretion-rate

A. These tests were done before and after the administration of a pyrogen in 15 patients who had had no antibiotic treatment within the previous month:

Urine-culture.—The urine was definitely infected in 7 of the 15 patients; in 2 others the few organisms were considered to be contaminants, and in the remaining 6 the urine was sterile.

The control urinary white-cell excretion-rate was 400,000 per hr. or above in 9 of the 15 patients (fig. 4). In 4 of these whose white-cell excretion was above 400,000 and below 800,000 per hr. the urine was infected.

Pyrogen test.—After the intravenous administration of pyrogen the white-cell excretion-rate rose by more than 100%, and was greater than 400,000 per hr. in 11 of the 15 patients. All 4 patients who did not respond in this way had biopsy evidence of pyelonephritis, and in 2 of these the diagnosis was later confirmed at necropsy; at the time of the biopsy the glomerular filtration-rate in these 2 cases was 28 and 15 ml. per min. Of the other 2, case 21 had, as well as the positive renal biopsy, a renal calculus and a control white-cell excretion-rate of more than 1,000,000 per hr.

B. Urine culture and white-cell excretion-rate were also measured before and after a pyrogen was given in another group of 11 patients who had had a course of antibiotics within a month, though treatment had ceased at least three days before:

Urine-culture.—The urine was definitely infected in only

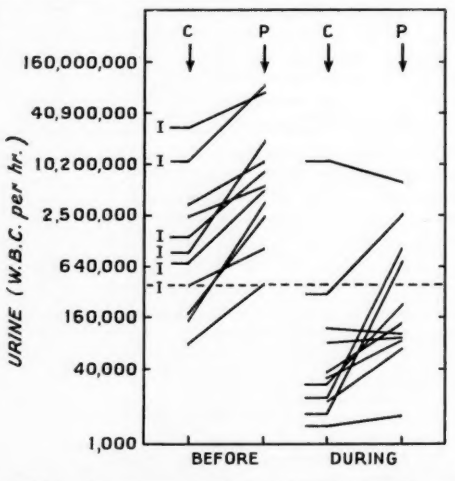

Fig. 6—Effect of treatment: urinary white-cell excretion-rate (C) before and (P) after administration of a pyrogen in a group of 11 patients before and during treatment with antibiotics.

The broken horizontal line indicates a rate of 400,000 per hr. I=patient with infected urine.

2 patients; in another the culture was contaminated and in the remainder the urine was sterile.

The control white-cell excretion-rate was greater than 400,000 per hr. in 6 of the 11 patients (fig. 4).

Pyrogen test.—After pyrogen was given 5 patients had a rise in urinary white-cell excretion of more than 100%, and a final rate of more than 400,000 per hr. 1 of these had a normal control excretion-rate. Thus only 4 of the 11 patients in this group had a white-cell excretion-rate which was normal before the pyrogen was given, and which did not rise above 400,000 per hr. thereafter.

Arterial Pressure and Creatinine-Clearance

14 of the 26 patients with chronic pyelonephritis had a diastolic arterial pressure between 95 and 160 mm. Hg. 4 of those with a diastolic pressure of 90 mm. or below had biopsy evidence of chronic pyelonephritis. These included 2 patients in whom the histological lesions were described as " probable pyelonephritis ".

The creatinine-clearance was 60–25 ml. per min. in 11 of the 26 patients; 7 of these had positive biopsies. In the others the creatinine-clearance was greater than 60 ml. per min.

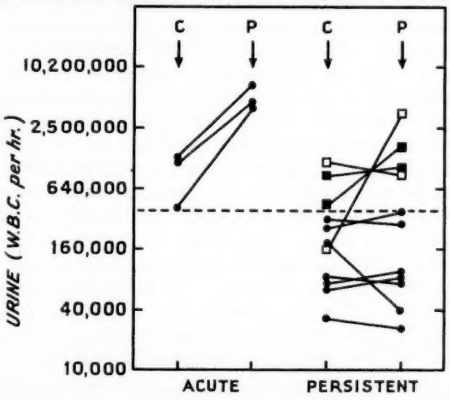

Fig. 7—Glomerular nephritis: urinary white-cell excretion rate (C) before and (P) after administration of pyrogen in acute and in persistent glomerular nephritis.

The broken horizontal line indicates a rate of 400,000 per hr. ● = histological evidence of glomerular nephritis. ○ = no biopsy. ■ = nephrotic syndrome with histological evidence of glomerular nephritis. □ = nephrotic syndrome without histological confirmation.

Fig. 5 shows that a rise in diastolic arterial pressure was not related to a fall in creatinine-clearance.

Further Observations

Some of the evidence presented above was from patients who had had treatment within the preceding month but which had ceased before the investigations were performed. The results showed that, though the urine was rarely infected, several patients still had a control white-cell excretion-rate greater than 400,000 per hr., and even more had a brisk rise in white-cell excretion-rate after administration of pyrogen. It was decided to study the white-cell excretion-rate and its response to pyrogen before and *during* treatment in the same patients:

11 patients who had not had treatment before the initial investigations were re-examined a week to three months later, having been given antibiotics every day during the interval. Treatment was continued throughout the day upon which the second set of observations were made.

The results before and during treatment are shown in fig. 6. Before treatment the urine was infected in 6 patients and the control white-cell excretion-rate was greater than 400,000 per hr. in 8. During treatment the urine was sterile in all patients, and 10 of the 11 patients had a control white-cell excretion-rate below 400,000 per hr.; after the pyrogen was given the change in white-cell excretion-rate was within normal limits in 7 patients but in 3 it rose more than 100% to a level greater than 400,000 per hr. The other patient had a high control white-cell excretion-rate which fell slightly after the pyrogen.

Pyrogen Test in Glomerular Nephritis (fig. 7)

Acute glomerular nephritis.—A pyrogen test was performed in 3 patients with acute glomerular nephritis confirmed by biopsy. The control white-cell excretion-rate was greater than normal, and rose by more than 100% in all of them.

Persistent glomerular nephritis.—In this group there were 11 patients. The diagnosis was confirmed by biopsy in 9. 7 had proteinuria which did not exceed 3 g. per day whereas in the other 4 it was more than 7 g. per day and was accompanied by œdema and hypoproteinæmia.

The control white-cell excretion-rates in the 7 patients with moderate proteinuria were all below 350,000 per hr., and after the pyrogen was given none rose above 400,000 per hr. Of the 4 patients with severe proteinuria the control white-cell excretion-rate was greater than 400,000 per hr. in 3; after pyrogen the rate rose from 455,000 to 1,760,000 per hr. in 1 patient, and from 185,000 to 3,640,000 per hr. in another, while in the other 2 it did not change materially.

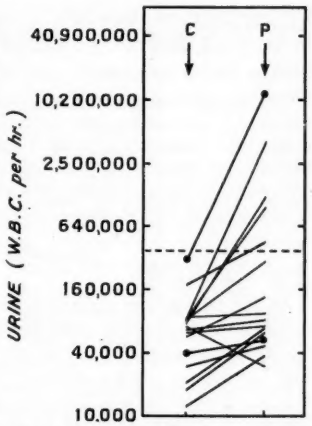

Fig. 8—Hypertension: urinary white-cell excretion-rate (C) before and (P) after a pyrogen in 16 patients with essential hypertension.

The broken horizontal line indicates a rate of 400,000 per hr. ● = histological evidence of glomerular nephritis.

Pyrogen Test in Essential Hypertension (fig. 8)

The 16 patients in this group had sustained diastolic pressures of 110 mm. Hg or more; 7 of the 16 had a diastolic pressure greater than 140 mm. All had a normal I.V.P. Renal aortograms performed in 5 patients showed no unequivocal abnormality. Renal biopsies in 2 were both normal. The creatinine-clearance was 55 ml. per min. or more in 14 of the 16 patients, and the urine concentration tests in 11 patients were all normal except one. 9 patients had a trace to + of protein in the urine; the others had no proteinuria.

No patient gave a history of previous urinary infection. 1 with a normal biopsy (fifteen glomeruli) had had acute glomerular nephritis three years before.

The control white-cell excretion-rate was 372,000 per hr. in 1 patient, and below 200,000 per hr. in the other 15. After pyrogen the change in white-cell excretion-rate was within normal limits in 11 of the 16 patients; in the other

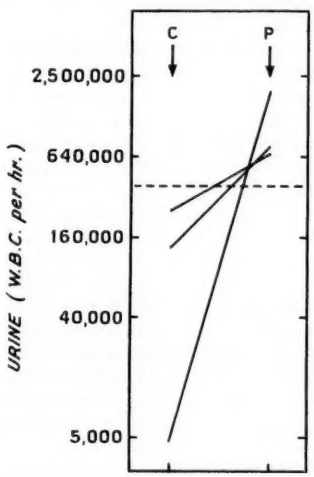

Fig. 9—Acute urethritis: urinary white-cell excretion-rate (C) before and (P) after administration of pyrogen in 3 patients with asymptomatic proteinuria associated with non-gonococcal urethritis.

The broken horizontal line indicates a rate of 400,000 per hr.

5 it rose by more than 100% to rates of 460,000, 700,000, 1,200,000, 3,300,000, and 12,000,000 per hr.

Pyrogen Test in Urethritis

The pyrogen tests in 3 young men who had asymptomatic proteinuria on waking are shown in fig. 9. Urethritis was diagnosed by examining an early morning urethral smear. In each patient the control white-cell excretion-rate was within normal limits; after pyrogen was given it rose by more than 100% to a rate greater than 750,000 per hr.

Discussion

Acute Pyelonephritis

In the 15 patients studied the onset of acute symptoms was five to ninety days (average twenty-eight days) before the observations recorded here were made, and all patients had previously been treated with antibiotics. The clinical diagnosis was that of acute " pyelitis ". The findings therefore give information on " treated " acute " pyelitis ".

The most striking finding was that nearly a third of these patients, who were considered to have nothing more serious than acute pyelitis, had gross acute pyelonephritis involving the cortex. The biopsy specimens contained only cortical material, but it is probable that the changes in the medulla were also extensive and severe; this conclusion is supported by the findings in the nephrectomy specimen from case 5. Considering the focal nature of the disease, therefore, extensive cortical and medullary lesions are very likely in more than 30% of patients with acute " pyelitis ". In some these advanced structural changes did not alter the appearances of an I.V.P. It follows that in a patient with an acute upper urinary infection a normal I.V.P. is no guide to the presence or extent of the structural damage. Moreover, after pregnancy the interpretation of an abnormality in the I.V.P. is difficult, because the residual physiological changes may resemble those of acute infection (Kretchmer et al. 1933). It is surprising that these acute severe structural cortical lesions may be present without proteinuria.

The antibiotic treatment generally given to patients with acute upper urinary infections may not sterilise the urine, and even when it does there is often continued evidence of residual inflammation. Either the rate of white-cell excretion continues high or it can be stimulated to abnormally high levels by the injection of pyrogen. Urinary white-cell excretion-rates and the use of pyrogen are rarely of value during the acute phase of an upper urinary infection, for the white-cell excretion-rate is usually very high and may be astronomical (e.g., greater than 250,000,000 per hr.). They can be helpful later, however, when as a result of treatment the urine is sterile and its content of white cells appears normal. A high control white-cell excretion-rate at this time, or a brisk rise after pyrogen is given, will then reveal that inflammation is persisting and that treatment should continue, or in some patients with a vague history, in whom antibiotic treatment has been started without proper examination of the urine, similar observations will support the original diagnosis.

Chronic Pyelonephritis

In chronic pyelonephritis there may be no history of previous renal infection, a normal I.V.P., no proteinuria, a normal blood-pressure, or a normal creatinine-clearance and ability to concentrate. Biopsy evidence of chronic pyelonephritis was obtained in patients with a normal I.V.P. and no previous history of urinary infection. Conversely, the biopsy was sometimes normal in patients with a clinical history and I.V.P. which strongly suggested chronic pyelonephritis. In a few patients the urine was sterile though the white-cell excretion-rate showed that inflammation continued, in others the urine was infected but evidence of inflammation was lacking. Such paradoxical findings emphasise how difficult it is to diagnose chronic pyelonephritis, and they illustrate the importance of using multiple methods of investigation when it is suspected.

The value of renal biopsy is limited by the focal nature of the disease. This is shown by the 4 patients with a history of upper urinary infection who also had abnormal I.V.P.s but from whom normal renal cortex was obtained. Weiss and Parker (1939) stressed the following points in the histological diagnosis of pyelonephritis: tubules containing colloid casts (thyroid areas), marked infiltration of intertubular tissues with lymphocytes and plasma-cells, periglomerular fibrosis, and the focal nature of the disease. 9 of the above patients were considered to have chronic pyelonephritis on these criteria. In 3 other cases which we termed " probable pyelonephritis " there were similar foci of chronic inflammatory cells in the renal cortex associated with occasional fibrotic glomeruli, but the lesions were less extensive and were not associated with " thyroid like " tubules. In these 3 cases the possibility arose that the lesions were solely the result of nephrosclerosis. The differential diagnosis between chronic pyelonephritis with scarring, and nephrosclerosis with lymphocytic infiltration secondary to ischæmia, may be difficult, but the extent and type of the inflammatory-cell exudate was considered too extensive for nephrosclerosis, particularly in case 27. In addition, case 26 had a history of recurrent upper urinary infections, I.V.P. appearances of pyelonephritis, and a normal blood-pressure; and case 25 had a history of recurrent upper urinary infections, particularly severe during pregnancy.

11 of the 12 patients with renal biopsy evidence of chronic pyelonephritis had proteinuria, whereas it was only present in 6 of the 14 patients without histological evidence of pyelonephritis but with a history of recurrent urinary infections and an abnormal I.V.P. The frequent absence of proteinuria was also mentioned by Kipnis et al. (1955).

6 of the 7 patients who had biopsy evidence of chronic pyelonephritis but in whom the I.V.P. was normal had a diastolic arterial pressure of 90 mm. Hg or more, but renal arteriograms suggested cortical scarring in 2 of these. Clearly in a patient with hypertension a normal I.V.P. does not exclude chronic pyelonephritis. In contrast, only 10 of the 17 patients with an abnormal I.V.P. had a raised blood-pressure. There was no correlation between blood-pressure and creatinine-clearance, which suggests that the rise in blood-pressure is not simply related to reduction in the number of nephrons. This is in keeping with the findings at necropsy, when it has often been shown that 30–60% of patients with chronic pyelonephritis have not had hypertension (Platt and Davson 1950, Kincaid-Smith et al. 1958).

In untreated chronic pyelonephritis the control-rate of urinary white-cell excretion was usually greater than 400,000 per hr. whether or not the urine was infected. Therefore a simple count of the control-rate of urinary white-cell excretion is, by itself, a most useful diagnostic

measure (Houghton and Pears 1957). A rate of 400,000 per hr. has been chosen as the upper limit of normal, but it is exceptional for a normal individual to have a rate greater than 200,000 per hr. The value of estimating the control white-cell excretion-rate is particularly important in those patients with rates between 400,000 and about 800,000 per hr., for in our experience routine methods for detecting an increase in the urinary content of white cells (i.e., counting the numbers per high-power field) usually give normal or equivocal results until the excretion-rate is greater than 800,000 per hr. In addition, some patients had a white-cell excretion-rate below 800,000 per hr. although their urine was infected. The absence of detectable increase in the content of white cells in the urine by routine inspection alone, therefore, does not absolve a routine laboratory from culturing the urine when requested to do so.

After giving pyrogen intravenously the urinary excretion of white cells in untreated chronic pyelonephritis usually rose by more than 100%, the eventual rate being greater than 400,000 per hr. A response such as this, in which there was both a 100% increase in white-cell excretion-rate and a final rate greater than 400,000 per hr., has therefore been arbitrarily defined as a positive pyrogen test. We would stress, however, that the pyrogen test was negative in 4 patients with biopsy evidence of chronic pyelonephritis. These negative responses are discussed below.

Of patients who had had treatment before admission to hospital the urine was infected in only 1 patient, but several had white-cell excretion-rates greater than 400,000 per hr. and positive pyrogen tests. This is in contrast to the results *during* treatment which were usually within normal limits. Further observations are needed, but these results suggest that even though antibiotics sterilise the urine viable organisms remain in the renal parenchyma.

All 3 patients with acute glomerular nephritis had positive pyrogen tests. But only 2 of the 11 patients with persistent glomerular nephritis had positive tests, and these may have been due to associated pyelonephritis. On the other hand, it is possible that on occasion nephrotic glomerular nephritis may give a positive test.

In the 16 patients with " essential " hypertension, 5 had a positive pyrogen test and in 2 of these the tests became negative after treatment with antibiotics. These results show that severe hypertension is not necessarily associated with a positive pyrogen test, and they suggest that the 5 patients with positive tests may have had an underlying renal infection.

One of the principal difficulties in interpreting the pyrogen test is to know whether a positive test indicates infective inflammation of the kidney, or of some other part of the urinary tract. In 3 patients not included in this series, in whom urinary infection was thought to be confined to the bladder, the control white-cell excretion-rate was raised but did not rise after the pyrogen was given. Katz (personal communication) has had similar results, but his findings are more convincing because his patients had acute hæmorrhagic cystitis confirmed by cystoscopy. There is no doubt, however, that asymptomatic urethritis in men gives a positive pyrogen test. Such patients usually present because proteinuria is found during routine examination. Further investigations reveal that though proteinuria is constantly present in the morning, it may disappear during the day; a paradoxical confirmation that the proteinuria is not due to parenchymatous renal disease. The diagnosis is easily confirmed by examination of an early morning urethral smear.

The finding that the pyrogen test is positive in acute glomerular nephritis as well as in pyelonephritis suggests that in renal disease the pyrogen increases white-cell excretion only when polymorphs are already present in the renal parenchyma. This is in keeping with the negative response of the 2 patients with chronic pyelonephritis who had advanced renal failure. Probably at this stage the inflammatory process is " burnt out ", and there are few, if any, polymorphs in the renal parenchyma. Katz also finds that in dogs with chronic pyelonephritis the pyrogen test becomes negative when the lesions are advanced. The increase in the rate of white-cell excretion in pyelonephritis and acute glomerular nephritis may be due to the passage of white cells already present in the peritubular space into the tubular lumen, or to a flare-up of the inflammatory process with a spilling over of newly arrived white cells. The speed and timing of the response suggests that movement of pre-existing white cells is more likely for the peripheral white-cell count does not rise for three or four hours.

The positive response in acute glomerular nephritis demonstrates that the increase in white cells is not a specific response of infective inflammation of the renal parenchyma. Nevertheless, in the absence of acute glomerular nephritis a positive pyrogen test is highly suggestive of infective inflammation of the urinary tract. This is further supported by the finding that a positive pyrogen test in chronic pyelonephritis usually becomes negative if it is repeated *during* the administration of an antibiotic. As in acute pyelonephritis, the pyrogen test appears to be the most sensitive means of assessing the efficiency of treatment, for it may remain positive after the urine has become sterile and the control urinary white-cell excretion-rate is normal.

Summary

The relation between certain diagnostic procedures in acute and chronic upper urinary infections has been studied.

Renal biopsies from patients with what is usually termed " acute pyelitis " have shown gross pyelonephritis of the cortex. Such patients may have a normal intravenous pyelogram and no proteinuria.

It has also been shown that evidence of chronic pyelonephritis on renal biopsy may be obtained from patients with a normal intravenous pyelogram and no previous history of urinary infections.

The urinary white-cell excretion-rate before and after administration of a pyrogen has been found useful both in diagnosis and in assessing the effectiveness of treatment.

Our thanks are due to Dr. R. W. Payne for his contribution in establishing the technique of the pyrogen test, and to Messrs. A. Wander, of Berne, for a supply of ' Pyrexal '.

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UREA IN THE MANAGEMENT OF HEAD INJURIES

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RAISED intracranial pressure after head injury may result not only from intracranial hæmatomas but also from local or general cerebral œdema, the combined effects of œdema, hæmorrhage, and necrosis around brain contusion or laceration, or from hypoxia where the airway is inadequate.

The concept that the phases of stupor and confusion after head injury were related to increased intracranial pressure led to treatment by dehydration and nursing the patient with the head raised to decrease the intracranial venous pressure. It is now generally agreed that intracranial pressure is not necessarily increased after head injury; this is so in the majority of cases, as Paterson (1943) pointed out. Except in selected cases therefore, where the intracranial pressure is known to be high, dehydration can do little good and it increases the risk of metabolic complications. Similarly the risks of inhalation from nursing an unconscious patient with the head up far outweigh the slight benefit from improving the venous drainage.

Where the intracranial pressure is known to be raised from causes other than an obvious intracranial clot, however, several measures can be tried to reduce it. Controlled dehydration for 2 or 3 days, by limiting the fluid intake and giving rectal infusions of saturated magnesium sulphate, is still useful in less severe cases. The use of tracheostomy has shown the importance of ensuring a free airway whatever else may be done, and this alone may be sufficient to restore the intracranial pressure to satisfactory levels. Hypothermia may also lower the intracranial pressure, particularly in cases with generalised cerebral œdema, although it is not uniformly effective. Craniotomy and bony decompression, where the compressing cause is focal from contusion of a frontal or temporal lobe, is valuable, particularly where damaged brain may be removed affording additional internal decompression. But not infrequently, where this procedure is particularly desirable, the brain may be so tight as to make operation difficult and cause risk of additional brain damage by opening the dura. For many years, therefore, a quick and effective hypertonic agent has been sought, which could help in this predicament. Intravenous hypertonic (50%) sucrose solution, and triple or quadrupled strength plasma (Hughes et al. 1938, Turner 1941) have helped from time to time, but in our hands neither has proved adequate when the need was greatest.

The use of hypertonic urea, usually given intravenously, to reduce brain bulk during neurosurgical operations, has already been described (Stubbs and Pennybacker 1960). Urea was introduced for this purpose mainly by Javid (1958), who followed a suggestion by Fremont-Smith and Forbes (1927). Javid confirmed that urea was superior to other agents in reducing intracranial pressure. We here describe our impressions on the use of urea in a pilot series of severe head injuries.

The Series

Between March 1, 1959, and May 31, 1960, a thousand and forty-six patients with acute head injuries were admitted to the accident service of the Radcliffe Infirmary, Oxford. Of these forty died, giving a mortality-rate of 4%. During this time twenty-seven patients received urea, either in a single dose to assist an operative procedure, or as treatment continued over some days, to control the intracranial pressure. Three other patients treated at the Army Neurosurgical Unit, Military Hospital, Wheatley, Oxon, were also given urea, making a total of thirty cases.

These patients had two features in common. All were comatose when treatment was begun, and all had considerably raised intracranial pressure with a tight brain, as seen at operation (fig. 1). In such a group the many factors involved—not only immediately relevant to the head injury but also to other injuries which many patients had sustained as well—precluded close analysis. But seventeen patients had intracranial clots of whom nine died; eight had severe bilateral brain injury, with seven deaths; three with generalised brain œdema and two with mainly temporal-lobe injury all survived. Thus sixteen lived and fourteen died. The severity of the cases under study may be gauged by the fact that six patients had stopped breathing at the time of operation. All were having such other treatment as seemed necessary for the head and other injuries. We record here the beneficial effects which we were satisfied were due to urea, and the complications. Experience with these cases has allowed us to modify the use of urea, as we shall explain.

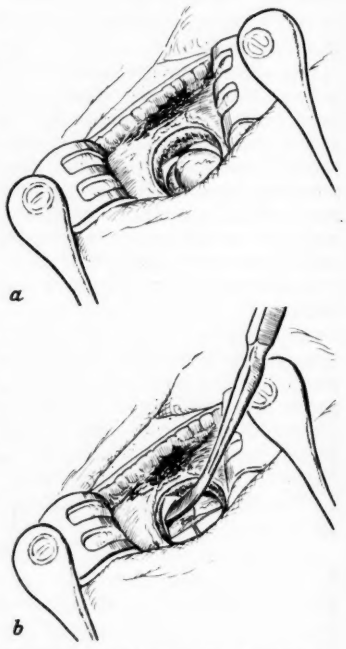

Fig. 1—Cerebral œdema after head injury: appearances at burr-hole exploration (*a*) before, and (*b*) 20 minutes after, intravenous urea.

Beneficial Effects of Urea

Reduction of Brain Bulk at Operation

Evacuation of a chronic subdural hæmatoma through appropriately placed burr-holes is usually simple, but the treatment of an acute subdural hæmatoma associated with brain contusion and laceration may be a very different matter. The brain swelling often prevents full evacuation of the clot by simple drainage, but even if this is achieved the decompression afforded is inadequate. Indeed, except in old people, an acute subdural hæmatoma often needs operation through a bone flap, with bony decompression. Reduction of brain bulk by means of urea may allow more

efficient evacuation of the hæmatoma, and even render a flap unnecessary:

A 20-year-old pedestrian was in coma, with decerebration and both pupils enlarging and becoming fixed (the left larger than the right), within an hour of injury. He had a left frontal scalp laceration without radiological evidence of skull fracture, but with fractures of the mandible and of the left ribs, and with a left pneumothorax. Immediate exploratory burr-holes revealed a left acute subdural hæmatoma. Urea 90 g. had been given intravenously immediately before operation, and the brain became very slack so that within half an hour it was easy to evacuate the hæmatoma through multiple burr-holes and unnecessary to turn a flap. The expected reactionary swelling of the brain was not seen at operation. The patient's general state improved immediately, the pupils becoming equal and reacting, though the increased tone in the limbs persisted. Urea 40 g. was given intravenously on the 1st and 2nd post-operative days, and 30 g. by mouth b.d. on the 3rd and 4th days once intestinal absorption was established. The patient was cooled to normal temperature, and early tracheostomy was performed. No further episodes of compression arose, and lumbar puncture showed a pressure of 270 mm. on the 4th day, and 170 mm. on the 6th day. 2 months after injury the patient was still mute, with a spastic quadriparesis.

Where cerebral compression is due to the combined effects of a thin layer of subdural clot and (mainly) œdema around an area of contused or pulped brain, the dura may be so tight that its opening is hazardous. Urea may make it possible to complete this kind of operation satisfactorily, and with far less risk to the normal or recoverable brain around the more obvious site of damage:

A woman pedestrian, aged 72, was admitted to hospital after a head injury, talking but confused. A left hemiparesis worsened, and 6 hours later she became deeply comatose. The pupils, which were normal on admission became barely reactive, the right being slightly larger than the left. The local head injury comprised a left frontotemporal scalp hæmatoma with underlying multiple left frontal fissured fractures and diastasis of the coronal suture. Exploratory burr-holes revealed a contre-coup right frontotemporal brain laceration, with œdema and some subdural hæmatoma. The dura was drum tight in the burr-holes, and the brain was swollen. Urea 90 g. was given intravenously during operation, permitting the flap to be turned and the dura to be opened easily. After the hæmatoma and necrotic brain debris had been removed the brain was slack and the left frontal cortex was some $^3/_4$ in. away from the dura. The clinical state improved immediately, the pupils being equal and reacting briskly, and the right limbs moving spontaneously. No further compressive episodes arose, and ventricular punctures subsequently showed atmospheric pressure. She developed left-sided focal fits and bronchopneumonia and died on the 6th day. Necropsy confirmed the findings at operation, with herniation of the right hippocampus, and midbrain compression with hæmorrhages.

Generalised Cerebral Œdema

This condition is seen from time to time after injury, particularly in children and young adults. In patients coming to necropsy the brain is severely and diffusely swollen, with internal herniations and without significant intracerebral or extracerebral hæmatoma or gross contusion. The bad prognosis which these cases have carried in the past has been improved by means of tracheostomy, which prevents the added effects of hypoxia, and more recently by the use of hypothermia (Lewin 1957). Decompressive operations in the past have failed uniformly because the brain has been so tight. One would expect a strong hypertonic agent, such as urea, to have its greatest effect in such patients. The three cases of this condition in this series have proved this to be so, all recovering. In the case described below urea treatment was combined with hypothermia, which alone had proved insufficient to deal with the pressure effects:

A child of 5, after a road accident, was deeply unconscious from the time of impact, with decerebrate rigidity and extensor plantar responses. The pupils reacted briskly, the right being slightly larger than the left. The temperature was 102°F. Skull X-rays showed no fracture, but there was scalp bruising in the right frontotemporal and occipital regions. He was treated by cooling to normal temperature, and fluids were restricted to 1 pint a day. The blood-pressure and pulse remained steady, and his condition was unchanged until 90 hours after injury when the right pupil dilated and became fixed, and the pulse fell to 40 per min. Respirations ceased as he was put on the operating-table, and recovered spontaneously after the initial burr-holes were made. Exploration showed an extremely tight brain everywhere, with no significant surface clot. When the dura was opened the brain swelled into the burr-holes, forming little mounds. When urea 30 g. was given intravenously the protruding brain became indrawn, and after half an hour it was pulsating in the frontal region, being some 3–4 mm. away from the dura. At the end of the operation the pupils were equal and reacting briskly. The patient's general state was good but he remained comatose. Hypothermia was induced to a temperature of 92°F.

Some 20 hours after exploration the right pupil again dilated and became fixed. 30 minutes later respirations ceased, both pupils becoming dilated and fixed. The patient was artificially respired and the heart beat continued, but the blood-pressure and peripheral pulses were unrecordable. Urea 30 g. was given intravenously over the next 30 minutes and spontaneous respiration returned within an hour of starting the infusion. 30 minutes later the pupils began to react, the blood-pressure was recordable, and his general condition had improved, although the body temperature had fallen to 85°F. For the next few hours his state was precarious, but this improved to the point where it was possible to perform exploratory posterior-fossa burr-holes to exclude any surface clot there, but only tight brain was found. Tracheostomy was performed, and a further urea injection was given intravenously during the next 24 hours, the lumbar-puncture pressure then being 100 mm. Urea 10 g. 6-hourly was given by mouth for a further 24 hours; a lumbar puncture 2 hours after the last dose showed sub-atmospheric pressure, and 30 hours later it was 65 mm. Meanwhile the papilloedema seen on the day of collapse became less. The general condition improved, with the left limbs responding to pain, and evidence of a right hemiplegia, although the tone was still increased in all limbs.

2 weeks after injury the patient opened his eyes and moved the left limbs spontaneously. Recovery was remarkable over the next few months; at 5 months he began to speak, smiling and recognising his parents, and at 6 months he began to walk. His mental performance was that of a child of $3^1/_2$ years. 10 months after injury, he could walk unaided despite some ataxia with weakness in the right limbs, and he was fully continent. His mental age was normal, and he had returned to school.

Postoperative Cerebral Œdema

After a decompressive operation there may be further clinical relapse on the 2nd or 3rd day, not from reaccumulation of intracranial clot but from developing œdema around the areas of brain damage. In some cases limitation of fluids together with rectal magnesium sulphate may prove adequate, and in others it may be possible to tap the cerebral ventricle. This last manœuvre is often o limited value after head injury, however, particularly in young patients where the ventricle is either small or impossible to find. An intravenous dose of urea in these circumstances may produce dramatic reversal of symptoms and gratifying improvement :

A 24-year-old car driver sustained a compound depressed right frontal fracture. Although he was able to talk at first, he became unconscious 45 minutes after injury, and at 6 hours

was totally unresponsive and decerebrate. The right pupil was then larger than the left, but both reacted to light. The patient was shocked, with a blood-pressure of 80 mm. Hg. Brain was discharging from the scalp wound. At operation the compound fracture was debrided, and a right frontal subdural hæmatoma with an underlying frontal intracerebral clot was evacuated. The brain was severely lacerated across the Sylvian fissure, with brisk hæmorrhage from branches of the middle cerebral artery which had to be clipped. Severe reactionary cerebral œdema developed during operation, but with the aid of urea 90 g. intravenously and tapping the left ventricle, the brain was slack at the end and the craniectomy could be closed easily. For the next 24 hours the patient's condition was better; he responded to simple commands, the pupils were equal and reacting, and the right limbs moved spontaneously. A further 60 g. of urea was given intravenously, but some of this ran interstitially causing severe swelling and erythema of the arm, with blistering at the site of the infusion at the wrist (fig. 2*a*).

40 hours after operation the patient's neurological state deteriorated, and he reacted in a decerebrate manner. The decompression was tight (the pressure at lumbar puncture was 330 mm.), but after urea 60 g. was given intravenously it became quite soft and slack. His general state improved, and he became more responsive. During the next 3 days urea 20 g. t.d.s. was given by mouth, and his condition continued to improve. 10 days after injury he began to talk, and at 3 weeks he was able to sit out of bed. He had a sensorimotor hemiplegia and hemianopia on the left. 4 months after injury he was mentally normal and speech was intact. He still had a left brachiofacial hemiplegia, but he could walk with a stick.

The Temporal-lobe Syndrome

Our observations on this series have been concerned principally with the comatose patient, but urea may prove helpful in at least one other group. Patients with bitemporal contusion remain stuperose for many days, with extensor plantar responses, and the pupils show transient inequalities. The site of damage is shown by the fracture lines or the local damage from impact. The picture is not of seriously advancing cerebral compression, and if temporal burr-holes are made no gross surface hæmatoma is found, but the brain at one or both sites is contused and tighter than normal. Most of these patients improve gradually under a regimen of limited fluids and rectal magnesium sulphate, but they cause a good deal of anxiety. There is always the risk that some added incident, such as too rapid rehydration or an intercurrent chest infection may lead suddenly to increased œdema of one temporal lobe, and fatal uncal impaction. In the future urea in small doses may bring these patients through more safely, although we have not yet used urea in this less severe group. But the case recorded below, with more severe temporal-lobe contusion, illustrates what may arise:

A 17-year-old cyclist, in a road accident, sustained left parietal skull fractures with an overlying scalp hæmatoma. She was unconscious from the outset. At first there was no reaction to pain, the pupils were small and fixed, and both plantar responses were extensor. Over the next 36 hours she slowly improved, moving all limbs spontaneously and responding briskly to pain, and the pupils were reacting. But 44 hours after the injury the *right* pupil became fixed and the tone was increased in all limbs, with a left hemiparesis. Later the pupils reacted once more. At 60 hours the *left* pupil became fixed and dilated and the patient was less responsive. Exploration revealed bitemporal-lobe contusion with a tight brain. In the right temporal region was much necrotic brain debris and a thin layer of subdural clot, which was evacuated through a craniectomy. Urea 26 g. was given intravenously, and with these combined measures the brain at the end of the operation was quite slack. The patient's general state was much improved, the pupils became equal and reacted briskly, and the right limbs moved purposefully. 12 hours later she began to groan, and 24 hours after this she obeyed commands and responded verbally. She went on to make an uninterrupted recovery, the left hemiparesis resolving. 2 months later she was well, the only neurological abnormalities being bilateral hyposmia and slight left-arm ataxy, with increased reflexes on the left.

Effect on Severe Brain Injury

Urea will clearly have its greatest effect where œdema rather than brain damage from contusion or laceration predominates, or where a sizeable intracranial clot, which may be removed surgically, has also contributed to the cerebral compression. We have also given urea to a number of patients with severe bilateral brain damage who had a period of clinical cerebral compression. Of eight such patients all were in coma from the outset, save one who was admitted to hospital after deterioration, with respiratory arrest for 2 hours. Exploratory operation was undertaken to exclude any remediable clot when there had been pupillary changes. Although it was possible to reduce the intracranial pressure, as confirmed at operation, by the use of urea, the reduction of brain bulk was by no means so dramatic as in " cold " neurosurgical operations, nor was there notable clinical improvement, although temporarily the pupillary reactions might improve or the breathing become more regular. Six of these eight patients died in the immediate postaccident period without ever regaining consciousness, another remained severely disabled for many months before succumbing to pneumonia, and the last patient is still alive but unconscious a month after injury.

With such severe injury one would try any measures likely to benefit but there is no evidence so far (as indeed one would expect) that urea is likely to reduce significantly the mortality in this group. Unless improvement in the first 24 hours is very obvious, therefore, there is little point in continuing urea treatment and running the added risks of its complications.

Complications

Interstitial Injection

A 30% solution of urea is highly hypertonic. If injected inadvertently into the soft tissues, it can cause considerable swelling of the limb and indeed sloughing and necrosis of the soft tissues. This happened in one of our patients, and another similar example has been recorded (Small 1960). In our case the urea was injected into a hemiplegic limb and sloughing resulted, which finally healed (fig. 2) but clearly the most careful precautions must be taken to avoid this calamity.

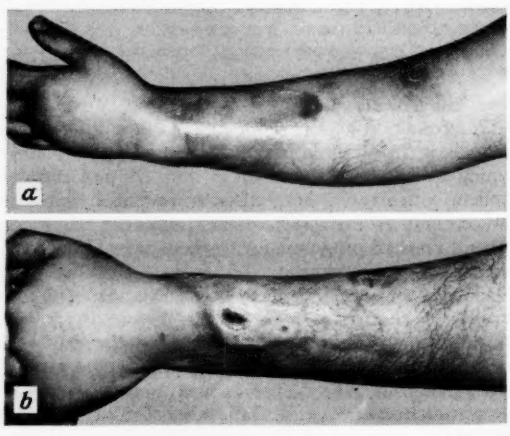

Fig. 2—Effects of interstitial injection of hypertonic urea (*a*) 24 hours after injection, and (*b*) 3 weeks later.

Thrombosis

Although it is true that an isolated intravenous injection of urea given into a healthy limb carries only a small risk of thrombosis, this is not so after a head injury. Soft-tissue injuries of the limbs are often present, and other intravenous therapy may be necessary. The more trauma a vein sustains the more likely is it that thrombosis will occur if a hypertonic irritant solution, such as urea, is given. Added to this is the increased risk of thrombosis if repeated injections of urea are given, as may be necessary after head injury, when, because of other injuries, the number of available veins is limited. These are the several reasons why six of our thirty patients had major thrombotic complications in the limbs, in one extending to the femoral vein, and in another to the common iliac vein.

Masking an Intracranial Clot

Such a powerful agent as urea, if given in the presence of an intracranial clot, might so reduce the surrounding œdema and improve the patient's condition enough to suggest that contusion and œdema had caused the compression; thus the clot would be missed. Apart from the need to establish the diagnosis of raised intracranial pressure by direct inspection before treatment with urea is begun, we think that at present preliminary exploration should be the rule before urea is used, to make as certain as possible that a remediable clot is not overlooked. In the following case both the brain swelling and the clinical state improved after a dose of urea despite a posterior-fossa extradural hæmatoma which was evacuated when the patient's condition indicated that further exploration should be made:

A 17-year-old epileptic boy fell from a ladder, sustaining a midline occipital fracture with an overlying scalp hæmatoma. He was unconscious from the outset; and, 6 hours later, the right pupil was slightly larger than the left but both were reacting, he was still deeply comatose, and the limbs were flaccid with absent plantar responses. Later a right hemiplegia was apparent in that he began to move his left limbs only. His condition deteriorated, with a falling pulse-rate, rising blood-pressure, and rising temperature, and with apnœa during transfer to the operating-theatre. Biparietal burr-holes showed an exceptionally tight brain with a small left subdural hæmatoma, and at ventricular puncture the pressure was very high. These measures restored spontaneous respiration. A left lateral bone flap was now turned, through which the brain began to bulge. Urea 120 g. was given intravenously, and this with continued ventricular drainage slackened the brain enough for the flap to be closed after inspecting the left hemisphere and finding no gross laceration. Bioccipital holes were then made; the right one showed some stripping of the dura and a thin layer of extradural clot, which was not thought significant as the dura was very slack.

After operation the patient's physiological state was greatly improved but his neurological state was not significantly changed. He was cooled to normal temperatures, and tracheostomy was performed. 24 hours after injury his condition again deteriorated, with periodic respiration, the right pupil dilated and fixed, and bilateral papillœdema. Ventricular puncture showed a pressure exceeding 600 mm., and after infusion of a further 90 g. of urea the pupils became normal again and the respirations were steady. A right carotid angiogram then showed no lateral shift, but suggested hydrocephalus. 28 hours after the first operation posterior-fossa exploration revealed a large midline extradural hæmatoma, with a tear in the dura and laceration of the cerebellar vermis. The clot was evacuated, and measured 5×2 cm. Afterwards the patient moved all his limbs to pain. Over the next 3 days further urea was given because daily ventricular punctures indicated high pressures of 300–180 mm., but there were no further compressive episodes. On the 6th day the patient opened his eyes and moved the left limbs well, a right hemiparesis remaining. At 3 weeks he obeyed commands. His later progress has been slow, but continues. At 6 months he was still disorientated and doubly incontinent, with a mild right hemiparesis and some dysphasia.

It follows from this experience that urea could well be used as a stopgap whilst preparations for exploration are made after diagnosing an intracranial clot. But we would emphasise that, if urea were given in the first few hours after head injury, without the intracranial pathological process having been ascertained by exploration, a developing intracranial hæmatoma might well increase disastrously.

Circulatory Collapse

In two patients, one with evidence of cardiovascular disease and the other with diabetes, intravenous urea produced clinical neurological improvement, but, at the same time, symptoms of shock, with considerable fall in blood-pressure and increased pulse-rate. Both recovered, and we cannot with certainty incriminate the urea injection. But if urea is responsible it may be that, in patients with diminished cardiac reserve, the hypertonic solution causes a sudden increase of circulating fluid volume.

Metabolic Disorders

Dehydration, an obvious danger of prolonged treatment with urea, was seen in two of our cases. The probable sequence of events is that on the 1st day urea is given diuresis is so full that the output is far above the intake for that day. If urea treatment is continued for the next 2–3 days (although the urinary output will be less and may be close to the intake) the initial deficit is not made up, and this, with extrarenal losses, may produce progressive dehydration. Symptoms may arise very quickly, with a dangerous fall of blood-pressure, when compensatory mechanisms break down:

A man of 54 sustained a head injury, with a left temporal fissure fracture of the skull, and overlying scalp bruising. He was unconscious at first but was in a state of mental confusion, without focal neurological signs, on admission to a nearby hospital. 3 hours after the injury he again became unconscious, with the left pupil dilated and fixed, and by 5 hours he was decerebrate with a right hemiplegia. After transfer to the Radcliffe Infirmary immediate operation revealed a left middle-fossa extradural hæmatoma, which was evacuated. The brain re-expanded to fill part of the cavity left after evacuation of the clot, but it was not tight at closure. The improvement after operation was limited, the patient now responding to pain and groaning, but remaining decerebrate with a right hemiplegia. Next day although neurologically he was no worse the decompression was bulging and lumbar puncture showed a pressure exceeding 300 mm. Urea 60 g. was therefore given intravenously with resultant slackening of the decompression. For the next 24 hours his state was unchanged, but after a lumbar puncture, which again showed a pressure of 300 mm., the right pupil became fixed to light episodically, the level of consciousness deteriorated, the blood-pressure fell, and respiration became weak. A further 90 g. of urea was given, with immediate improvement in the clinical state and blood-pressure. The cranium was re-explored. No clot had reaccumulated, the brain being flush with the dura but not protuberant. At ventricular puncture the pressure was 160 mm. After this operation the patient again groaned and moved in response to pain. A further infusion of urea 45 g. was given next day, and the blood-pressure started to fall, with a narrowing pulse-pressure and rising pulse-rate, although the neurological state did not change. Daily estimates of the blood-urea had shown a progressive rise to 149 mg. per 100 ml. as would be expected, but the plasma-chloride had risen from 96 to 104 mEq. per litre, and the serum-sodium from 134 to 151 mEq. per litre. Because these physiological and biochemical changes suggested excessive dehydration, an intravenous drip was set up. The blood-pressure recovered immediately, and the pulse-rate fell

from 120 to 80 per mm. Slow improvement in the physiological and neurological state then continued.

A week after injury the patient began to speak, and he was transferred for rehabilitation after a month, when the right hemiplegia had improved so much that he could walk with help. He still had a partial left third-nerve paresis and some dysphasia. At 7 months the third nerve had recovered, and the right hemiparesis was very slight.

So far we have not seen other metabolic disorders with urea treatment, but closer study is clearly needed. In general we have not given urea where there was evidence of impaired renal function. Further urea should not be given as long as the blood-urea at the end of the effective period after injection is over 200 mg. per 100 ml. Complications could also arise where there is potential hepatic insufficiency. Walser and Bodenlos (1960) showed that much of the total body-urea is continuously being broken down by intestinal bacteria; this might increase with rise of the blood-urea, and if the liver were unable to deal with the reabsorbed nitrogenous breakdown products hepatic coma might be precipitated.

These observations on hepatic and renal function are relevant because so many patients with severe head injuries have other severe injuries as well, and the whole patient should be carefully assessed before treatment with urea is begun.

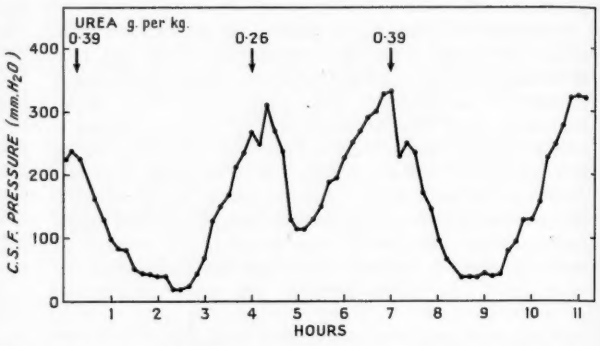

Fig. 4—Cerebrospinal-fluid pressure responses to small doses of urea by mouth.

The patient was a woman of 77, and treatment was started 45 hours after head injury, when the blood-urea was 45 mg. per 100 ml.

Technique of Administration

Urea for intravenous use is now available commercially*:

Two bottles are supplied, together with a polyethylene infusion set and a transfer set; one bottle contains 90 g. of urea crystals, lyophilised, and the other contains 210 ml. of 10% invert sugar. The resultant solution contains 30% urea in 10% invert sugar. Invert-sugar solution was found to be the best agent for dissolving urea crystals, and it is without risk of significant intravascular hæmolysis (Javid 1958). Urea crystals are stable, but the solution should be prepared immediately before use and discarded if not required within 24 hours. Warming aids solution, and preparation for intravenous use usually takes about 20 minutes.

Our experiences show that special care is needed during the intravenous infusion of urea. Where possible it should be given by needle venipuncture, the needle being passed well into the vein and fixed securely to the skin. The limb should be raised slightly to avoid distension of the veins above the injection site and to encourage the urea to mix rapidly with blood coming from other tributaries. Any tourniquet effect proximal to the infusion must be avoided so that the substance is not held in the limb. Where possible, further infusion should not be given through the same vein. If a cut-down is necessary the standard metal cannula should not be used because this can lead to a high concentration of urea in one part of the vein with almost inevitable thrombosis. It is better to use a long smooth-tipped polyethylene catheter which is passed into the vein for about 8 in. (fig. 3).

* 'Urevert', Baxter Laboratories, Ltd., 26, Great Tower Street, London, E.C.3.

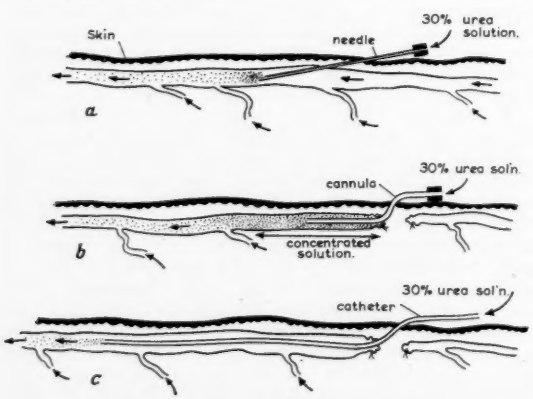

Fig. 3—Technique of injection (see text).

Comparison between (*a*) simple needle venepuncture, (*b*) " cut down " and cannulation, and (*c*) " cut down " and catheterisation.

Urea is normally given at about 60 drops per minute, although for a rapid effect—e.g., at operation or as a temporary supportive measure—the whole dose can be given in about 15 minutes.

In the acute stages of head injury the intravenous route is invariably used, but for continued treatment when gastric feeding is established, urea can be given effectively by mouth. The following formula has been found useful:

Urea *B.P.*	300 g.
Syrup simplex	300 ml.
Add water to 1000 ml.	

It is convenient to make up 1 litre of solution at a time and store it at low temperatures. It should not be used after 7 days from preparation. We have not found it possible to give urea by mouth until 3 or 4 days after injury, since in severe cases, gastric function is not infrequently impaired. Javid and Settlage (1956) and Javid (1958) have shown that urea is effective when given by gastric tube, and our experience is in general agreement with this. Even comparatively small doses have sometimes resulted in very obvious reduction of intracranial pressure (fig. 4).

Dosage and Administration

A full intravenous dose of urea is 1·5 g. per kg. body-weight, although if urea is likely to be effective after head injury, 1 g. per kg. will probably be sufficient. Before giving it a sample of blood should be taken for hæmatocrit and blood-urea estimation.

When for cerebral œdema it is decided to continue urea treatment over some days, only sufficient urea should be given to control excessive intracranial pressure, avoiding great reduction of pressure which, theoretically at least, might precipitate fresh intracranial bleeding. In general the total daily dose of urea should be kept below 1·5–2 g. per kg., its effectiveness being judged by the state of the decompression, or by lumbar or ventricular puncture as seems appropriate. A dose of urea given intravenously may be effective for 6–10 hours, and we have therefore continued urea treatment in divided doses at

8–10 hourly intervals, giving 0·5–0·7 g. per kg. according to the severity of the pressure problem. Once gastric feeding is established urea may be continued in doses of 20–30 g. 8-hourly. Because most of these patients are incontinent catheterisation to combat retention is unnecessary, but some means of accurately collecting the urine is required, so that closest attention may be paid to fluid balance during treatment. Our policy has been to maintain the fluid intake at about 3 pints a day and to keep carefully balanced intake and output charts. In addition the blood and urinary urea and choride, together with blood sodium and potassium and hæmatocrit, are estimated daily. During intravenous treatment the blood-urea is measured each 8 hours, before the next dose is given.

Mechanism of Action

Stubbs and Pennybacker (1960) suggested that a blood-brain barrier effect (whereby urea enters brain much more slowly than other soft tissues) best explains the mechanism of the action of urea, and that the effects observed are due principally to reduction in brain bulk. This reduction results from water loss. If urea passes into brain much more slowly than into other soft tissues, then while a concentration difference between plasma and brain urea is maintained water is withdrawn osmotically from the brain.

Observations on the rate of entry of urea into muscle compared with its rate of entry into normal brain in man lend support to this hypothesis (to be published). Investigations have shown that the blood-brain barrier is impaired or even abolished in traumatised brain (Broman 1949, Bakay 1955). Therefore one would anticipate little shrinkage of damaged brain substance. The fact that we observed striking reduction in brain bulk, even in severe cerebral injury, indicates that if there still remains a large enough volume of brain in which the normal barrier functions are preserved urea will act. Thus its dramatic effect in acute cerebral œdema can be explained.

Such a hypothesis could have two important implications in relation to the use of urea after head injury. In the acute phase, where there is no surgical decompression, it would be possible with enough urea to reduce the intracranial pressure to less than atmospheric, with the consequent risk of hæmorrhage from damaged vessels in the contused areas. It is also possible in the case of a polar contusion producing local deformity, that urea could, by shrinking the more normal brain on the opposite side, encourage any shift of the midline structures that may be present.

Conclusions

Observations of several workers leave no doubt that urea is the most potent agent in reducing brain bulk. It is most effective on normal brain as an aid to operative exposure, or when a tumour is present but the greater part of the brain is normal. Our findings suggest that it also has a place in the treatment of head injury, but it is not surprising that its beneficial effects are limited.

Urea may be used in the management of head injuries as an aid to decompressive procedures, and for long-continued treatment in the small group of patients where generalised cerebral œdema is the main factor. It carries particular dangers when intracranial bleeding is present, and when an intracranial clot is developing or suspected. Its use in these circumstances, except as an immediate preoperative measure, is to be deprecated. Indeed we feel that the intracranial state should always be determined by burr-hole exploration before urea treatment is begun.

The complications of urea so far are not so formidable as would at first appear; for these patients were gravely ill from the outset, and many had multiple major injuries in addition. We hope that with greater familiarity with urea the contraindications will be more firmly established. But it seems clear that there is no indication for urea treatment in the great majority of head injuries which, with simpler measures, will recover. Moreover, so far there is no evidence that urea will produce dramatic benefit in the group with widespread bilateral contusion and laceration, with coma from the outset. Urea can, however, clearly confer considerable benefit in selected cases.

Summary

The use of urea solution as a hypertonic agent to control intracranial pressure in a series of thirty severe head injuries is described, and a possible mechanism of action of urea is discussed.

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ALIMENTARY LIPÆMIA AND ISCHÆMIC HEART-DISEASE

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STUDIES on age-matched men have revealed that following fat-feeding, lipæmia is more intense and more long-continued in patients with ischæmic heart-disease than in controls (Barritt 1956, Bronte-Stewart and Blackburn 1958, Mitchell and Bronte-Stewart 1959).

The extent and duration of postprandial lipæmia after a standard fat meal can depend on the nature of the dietary fat intake before the test (Pomeranze et al. 1954, Bronte-Stewart and Blackburn 1958). On the other hand, differences between patients and controls have been found in hospital patients, who had all been on a normal hospital diet for some time before the test (Mitchell and Bronte-Stewart 1959). In Cape Town there reside three racial groups with distinct differences in their customary dietary fat intake: the Bantu, consuming approximately 17% of their total calories as fat; the Cape Coloured, approximately 25%; and the European, approximately 40% (Bronte-Stewart, Keys, and Brock 1955). We set out to determine whether the degree of lipæmia following the feeding of fat differed between these racial groups and to compare the findings with those obtained in age-matched patients with ischæmic heart-disease.

In addition the findings following the administration both orally and intravenously of a fat emulsion to a small group of patients with ischæmic heart-disease were compared with those observed in age-matched controls.

Subjects Studied

Altogether 146 males between the ages of 20 and 59 years underwent an oral fat-tolerance test. All were ambulant and actively engaged in their customary occupations. 29 had

clinical and electrocardiographic evidence of previous myocardial infarction and formed the group designated as patients. The controls, consisting of 45 White, 39 Cape Coloured, and 33 Bantu, were apparently healthy, and had no clinical or electrocardiographic evidence of ischæmic heart-disease. Both patients and controls had blood-pressure levels within the accepted normal range.

For the intravenous fat-tolerance test patients in hospital were used. 7 male patients recuperating from recent myocardial infarction were matched for age and weight with 7 male controls, convalescing from respiratory infection. These controls had no clinical or electrocardiographic evidence of ischæmic heart-disease.

Methods

Oral-fat-tolerance Test

After an overnight fast of 12 hours, the test-meal was given. It contained 70 g. of butter-fat, and was fed in the form of a breakfast: 1 oz. cereal, 6 oz. fruit juice, 2 oz. bread, 2 oz. butter, 20 oz. milk, and $^1/_2$ oz. sugar. This provided 1256 calories. The subjects were instructed not to drink water before the meal or during the test. Those who wished to smoke were permitted to do so. Personal supervision ensured that the meal was consumed completely. Venous blood was obtained before the test breakfast was given (the fasting sample) and then again at 2, 4, 6, and $7^1/_2$ hours after completion of the meal. On each occasion 9 ml. of blood was added to test-tubes containing 1 ml. of freshly prepared 3·8% sodium citrate.

After the test was completed the blood was centrifuged at 3000 r.p.m. for 8 minutes. The plasma was separated and incubated at 37°C in a water-bath for at least 15 minutes, and read immediately thereafter. The degree of lipæmia was estimated by measuring the optical density of the plasma in a Klett-Summerson photoelectric colorimeter using a red filter (no. 66) and a distilled-water blank. Results are expressed in terms of the direct scale readings in turbidimetric units.

The degree of lipæmia (in turbidimetric units) was plotted against time, and a curve obtained. The area under this curve was then calculated by the method of counting squares, the results being expressed as the total area (in sq. mm.) for each curve. This gave some indication of the quantity of fat circulating during the postprandial period (Gage and Fish 1924, Burr et al. 1954).

Intravenous-fat-tolerance Test

Each pair, a patient and his matched control, were tested together. In some pairs the fat was first administered orally and then intravenously; but in other the procedure was reversed, the intravenous tolerance test being performed first.

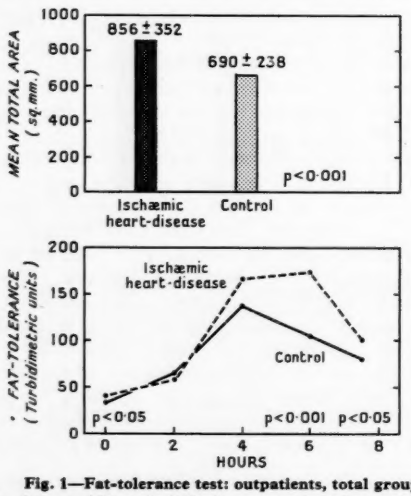

Fig. 1—Fat-tolerance test: outpatients, total group.
The degree of lipæmia following a standard fat meal was more intense in patients with ischæmic heart-disease (n=29) than in age-matched controls (n=24).

After an overnight fast, venous blood was withdrawn, and the fat (600 ml. of 'Lipomul I.V.' *) fed orally over a period of half an hour. Thereafter the same conditions as for the butter-fat tolerance test applied; blood being withdrawn after 2, 4, 6, and $7^1/_2$ hours.

For the intravenous test, after an overnight fast the emulsion (600 ml.) was administered intravenously over a period of 2 hours. Initially the rate of flow was 10 to 15 drops per minute, but after half an hour this was increased to 45 drops per minute. For the last hour the rate was 100 drops per minute. On completion, the infusion apparatus was removed, and the patient remained in bed for the remainder of the test. Venous blood was tested 1, 2, 3, 4, and 6 hours after completing administration of the fat.

All blood samples were treated in the manner described for the oral-fat-tolerance test.

Results

Oral-fat-tolerance Test

The comparison of the two age-matched White groups —one with and the other without ischæmic heart-disease— showed that in males with established ischæmic heart-disease there was a greater and more long-continued postprandial lipæmia than in age-matched control subjects (see fig. 1). This difference was manifest mainly at the 6-hour and $7^1/_2$-hour periods, at which times the difference between the two groups was highly significant. A finding of great interest was the small but significant difference in fasting lactescence, patients with ischæmic heart-disease having a greater fasting lactescence.

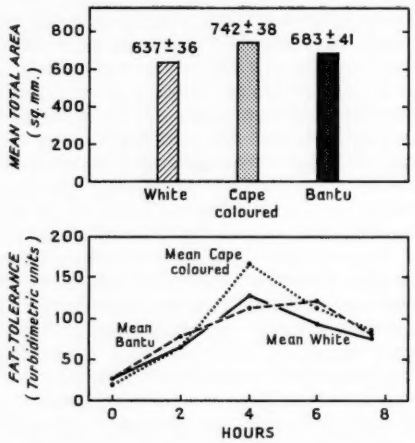

Fig. 2—Fat-tolerance test: outpatient controls by race.
Despite pronounced differences in their customary fat intake the three racial groups showed no significant differences in the degree of lipæmia following a standard fat meal.

Racial differences.—The results for the controls in the three racial groups are compared in fig. 2. These results revealed that there were no differences between the three racial groups in their tolerance to a test-meal of fat.

The effects of age.—Comparison on controls over the age of 40 years, with those below that age showed that age did not influence the extent of the alimentary lipæmia following the test-meal (fig. 3).

* The formula for lipomul I.V. is as follows: cottonseed oil 15% w/v; dextrose anhydrous 4% w/v; lecithin 1·2% w/v; oxyethylene-oxypropylene polymer 0·3% w/v. The emulsion was kept refrigerated but not frozen. It is made by the Upjohn Company, Kalamazoo, Michigan, and provided as a sterile emulsion of 600 ml. The fat globules are predominantly 0·5 to 1 μ in diameter, and 1 bottle provides 80 g. of fat.

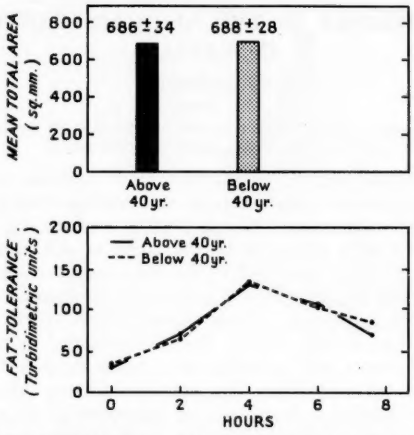

Fig. 3—Fat-tolerance test: outpatient controls by age.
Comparison of individuals below the age of 40 years (n=69) with individuals above the age of 40 years (n=48) failed to show any differences in the degree of lipæmia following a standard fat meal.

Intravenous-fat-tolerance Test

The pattern of the oral tolerance curves followed closely those obtained in the butter-fat tolerance tests. There was a delayed lipæmia in the patients, significant differences ($P < 0.05$) from the controls being recorded after 6 and $7\frac{1}{2}$ hours (fig. 4).

When the emulsion was administered intravenously, no difference in degree of lipæmia or rate of removal was found between the patients and controls (fig. 5).

Discussion

In this study patients with ischæmic heart-disease exhibited a more intense and more long-continued lipæmia than age-matched controls when fed fat, whether this was butter containing a large proportion of saturated fatty acids or cottonseed oil, with a high content of unsaturated fatty acids. The study was conducted on ambulant individuals performing their daily work; so the customary level of fat intake, from the quantitative aspect, immediately before the test and more remotely, does not appear to affect the type of lipæmic response, since identical responses were found in the samples from the different racial groups residing in Cape Town.

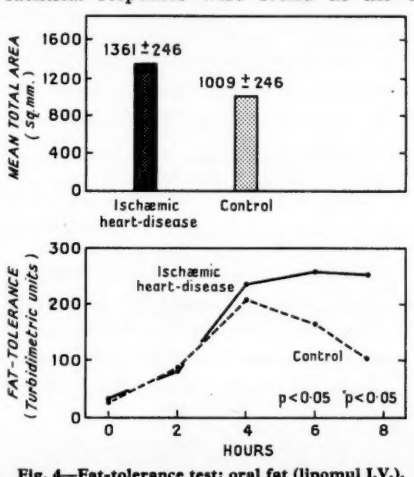

Fig. 4—Fat-tolerance test: oral fat (lipomul I.V.).
An intravenous fat emulsion when fed orally produced more intense lipæmia in patients with ischæmic heart-disease than in age-matched controls.

The degree of lipæmia at any one time reflects not only the rate of absorption from the gut but also the rate of removal of fat from the plasma. As the differences between patients with ischæmic heart-disease and controls in most studies are greatest in the later postprandial phases, attention has been directed to fat-clearing mechanisms as the reason for these differences. Certain workers using heparin to activate clearing have claimed that defective clearing is responsible for these effects (Block et al. 1951, Oliver and Boyd 1953, Herzstein et al. 1954). On the other hand similar in-vivo studies (Hood et al. 1954, Kaufmann 1955) revealed no differences which could be attributed to ischæmic heart-disease. Baker (1957), using coconut oil emulsion as the substrate, also could not detect any difference in clearing-factor activity between normal controls and patients with myocardial infarction. In a study on matched pairs, Mitchell and Bronte-Stewart (1959) used the lipæmic plasma of patients and controls as the substrate and incubated this in a four-way cross-over manner with the non-lipæmic plasma of each pair after administration of heparin. The lipæmic plasma was cleared at the same rate in each system. It was concluded

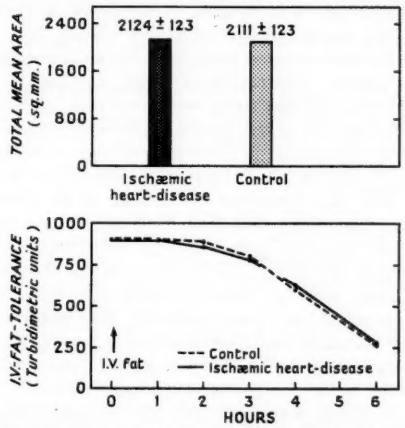

Fig. 5—Intravenous-fat-tolerance test (lipomul I.V.).
The intravenous fat emulsion when given intravenously failed to show any differences after administration to the same individuals as in fig. 4.

Rate of clearing: ischæmic heart-disease, 173 T.U. per hr.; controls, 174 T.U. per hr.

that the more intensive and more long-continued lipæmia in the patients could not be explained by differences in the physical or chemical state of the fat particles in the plasma following the feeding of fat, nor could the explanation lie in the heparin-activated enzyme system. Absorptive mechanisms should receive more attention, but there is still no evidence that the clearing mechanism activated by heparin is similar to that which operates naturally (Robinson and French 1953).

In the present study intravenously instilled fat was removed at an identical rate in all subjects, whereas, when ingested orally, the same amount and type of fat produced more pronounced lipæmic responses in the patients than in the controls. This could imply that the more intense and long-continued lipæmia in patients with ischæmic heart-disease is due to absorptive mechanisms. There are, however, certain difficulties in this interpretation. Variations in technique of administration, such as in the rate and duration of administration, could underlie the reported variations between individuals in the rate of removal of intravenously instilled fat (Mueller 1957, 1958, Bozian et al. 1957). In order to eliminate this possibility, a study was conducted on matched pairs, and an identical rate of infusion over the 2-hour period was ensured.

As it has been claimed that different fats have different

lipæmic responses (Eggstein and Schettler 1958) the fat emulsion had to be fed orally if comparison with the intravenous effects was to be undertaken. In this instance the plasma-fat-particle suspension need not be physico-chemically similar nor need the mechanism of removal of the fat from the plasma be similar for the different routes of administration. Iacono et al. (1960) however, found little difference in the chylomicron composition in their comparison of the plasma following oral and intravenous administration of a fat emulsion similar to the one used in this study.

The fat emulsion also contained an emulsifying agent which included 1·2% of lecithin w/v. These results could be interpreted as showing that the emulsifying agent in the fat emulsion supplied a factor which accelerated the removal of fat. This is unlikely for the following reasons: we would have to postulate that this factor was lacking in the patient group and not in the controls, and that it operated only when instilled directly into the circulation and not when given by mouth. Nevertheless as part of the emulsifying agent consists of phospholipids and certain phospholipids from soya bean have been claimed to clear lipæmic plasma (Schrade et al. 1959), this needs further investigation. In this study we noted that, although the same amount of fat was given orally and intravenously, the degree of lipæmia in both patient and control groups was much greater after intravenous administration; this feature was also described by Iacono et al. (1960). It could be due to the fact that chyle normally enters the circulation at a slower rate, although Berry and Ivy (1948) showed that chyle instilled intravenously is cleared much more rapidly than an artificial emulsion. In studies on earlier preparations of fat emulsion administered intravenously, Waddell et al. (1953) stressed that the emulsifying agent greatly influenced the rate of removal of the infused fat, while the chemical composition of the oil did not. It would appear therefore that the emulsifying agent is more likely to inhibit the clearing mechanism than to enhance it.

Summary

An oral butter-fat tolerance test was performed on 146 males: 29 patients with ischæmic heart-disease and 117 controls. The controls consisted of members of the three racial groups resident in Cape Town.

The alimentary lipæmia was greater and more long-continued in patients with ischæmic heart-disease than in the controls. A typical pattern of tolerance curve was found among the patients: greater fasting lactescence of the plasma and long-continued postprandial lipæmia in the patients with ischæmic heart-disease. No racial or age differences in the fat-tolerance test were demonstrated.

The combined study of oral and intravenous fat-tolerance tests was undertaken on 14 volunteers: 7 patients with ischæmic heart-disease and 7 controls. When the fat was fed orally the characteristic differences between patients and controls was observed. When the fat was administered intravenously, no differences in the amount of circulating fat or the rate of removal of the fat from the circulation were detected in the two groups.

This investigation was carried out in the Department of Medicine, University of Cape Town, as part of the programme of the clinical nutrition unit, under the direction of Prof. J. F. Brock, and was supported by the South African Council for Scientific and Industrial Research. It was also supported in part by research grant H-3316 (CI) from the National Heart Institute, Public Health Service, U.S.A. 'Lipomul I.V.' was kindly supplied by the Upjohn Company, Michigan, U.S.A.

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ATHEROMA IN THE AFRICAN (BANTU) IN NATAL

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A WIDELY accepted view is that atherosclerosis and its complications are less severe in the African than in the European. Laurie and Woods (1958), however, reported that, in Natal, atheroma of the aorta in Africans was widespread; and that cerebrovascular disease, which they implied was largely atherosclerotic, was at least as common as in the European. Later (Laurie et al. 1960) they also indicated that, though frank myocardial infarction was not often seen, ischæmic myocardial fibrosis due to coronary atherosclerosis was common among Africans. They believe that there is little difference in degree of atherosclerosis between African and European, other factors—such as decreased coagulability of blood—accounting for the lower incidence of myocardial infarction. From this it might be thought that the African in Natal differed greatly from Africans in other parts of Southern Africa. For this reason, we are presenting the results of an investigation into the racial incidence of atheroma in Durban, about 60 miles from where Laurie and Woods were working.

There are three major racial groups in Durban—African, European, and Indian—and we were able to make a direct comparison of the degree of atheroma in these three groups. African and Indian cases were from routine necropsies at King Edward VIII Hospital, and the European cases from routine necropsies at Addington Hospital, Durban. As far as possible, the tissues were collected from consecutive necropsies.

Method

The technique was that devised by Holman et al. (1958) at the Louisiana State Medical School. The aorta, from the level of the left subclavian artery to the bifurcation at the common iliac, was removed, opened longitudinally, dissected free from fat, and fixed flattened on cardboard in 10% formol-saline. The left coronary artery with its circumflex branch and the right coronary artery were opened with blunt-pointed iris scissors and dissected from the heart, adherent fat removed, and then allowed to stick to cardboard before fixation in formol-saline. The specimens were later stained with Sudan IV to demonstrate stainable lipid in the intima, and preserved in sealed plastic bags which permitted the vessels to be examined

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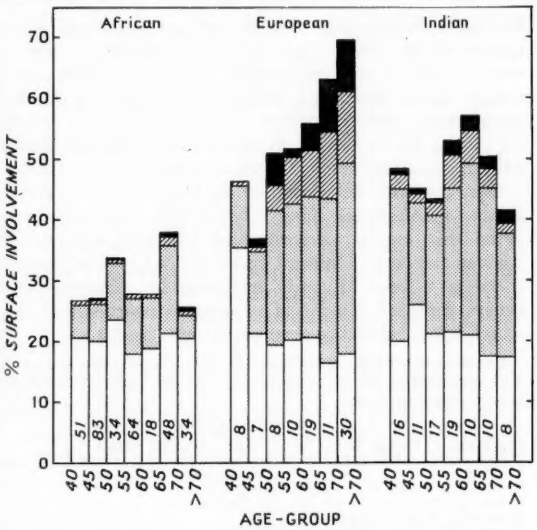

Fig. 1—Aorta: average percentage area of intima involved by atheroma in Africans, Europeans, and Indians.

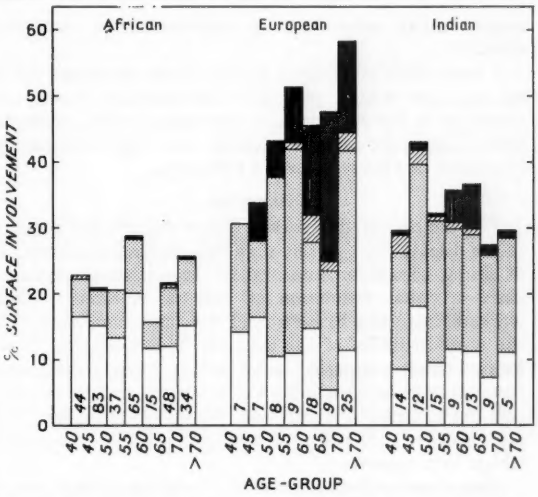

Fig. 2—Coronary arteries: average percentage area of intima involved by atheroma in Africans, Europeans, and Indians.

and handled conveniently later. Age, sex, race, and cause of death were recorded.

Cases were graded by estimating the area of intima involved by (*a*) fatty streaks, (*b*) elevated fibrous plaques, (*c*) lesions complicated by ulceration, hæmorrhage, or thrombosis, and (*d*) calcification. The estimations were simplified by considering the thoracic and abdominal aorta separately, and then summating the results—allowing for the thoracic aorta being roughly double the area of the abdominal aorta. The coronary arteries were similarly assayed. All specimens were graded by one observer.

Results

The main findings are given in figs. 1 and 2, illustrating, for each race, the average percentage of intimal surface involved by the different stages of atheroma in five-year age-groups above the age of 40. Younger age-groups are not included since we lack an adequate sample of European cases.

Cases of syphilitic aortitis, diabetes mellitus, nephrosis, and myxœdema have been omitted, since these conditions may have influenced the degree of atheroma. Exclusion of known hypertensives does not materially influence the findings, nor does separate consideration of males and females, so total cases are given. The groups of aortas and coronary arteries do not always correspond since it was not possible to retain both vessels in every case, and in others the specimen was incomplete and had to be discarded. While the point has not been investigated in detail, there does not appear to be a close correlation between the degree of atheroma in the aorta and coronary artery in any one person.

The results might be criticised on the grounds that the age of Africans may be inaccurate, but we feel the large number of African cases tends to lessen this error. A further criticism may be that European and Indian groups include cases of myocardial infarction—a common cause of death in the age-groups under consideration—though there were only 3 infarcts in the African series. The number of cases of myocardial infarction, however, probably reflects the incidence of severe atheroma in the population at large. Exclusion of myocardial infarction does not remove, though it may slightly reduce, the striking differences between the racial groups.

Europeans and Africans differed greatly in average area of intima involved and in severity of lesions, the Indians being intermediate. Plaque formation, ulceration, thrombosis, and calcification are all more extensive in the European than in the African group in each age-group (particularly in the very elderly); and this applies both to aorta and coronary arteries. An occasional African aorta may show severe atheroma—as severe as in a European—but there are many aortas from elderly Africans which are almost free of atheroma. The Africans came from both town and country, but we are not able accurately to separate these groups. In the aorta, the thick spongy atheromatous plaques which readily ulcerate are rare in the African. Nor do we see the completely calcified rigid coronary arteries, so common in elderly Europeans. This low incidence of severe atheroma in the African must be emphasised.

Though we were unable to compare the European and African under the age of 40, table I illustrates the African compared with the Indian. The values for fatty streaking in the African closely resemble those found in the survey conducted by Strong et al. (1959), when the Bantu was compared with the New Orleans white and Negro popula-

TABLE I—AORTIC ATHEROMA UNDER 40 YEARS: COMPARISON OF INDIAN AND AFRICAN

Age-group	Indian				African			
	Total cases	Average % area			Total cases	Average % area		
		Total	Fatty streaking	Fibrous plaques		Total	Fatty streaking	Fibrous plaques
16–20	13	22·8	22·8	..	11	20·0	20·0	..
21–25	10	23·8	23·8	..	33	22·3	22·3	..
26–30	7	43·8	42·6	1·2	40	27·2	25·0	2·2
31–35	13	35·3	34·5	0·8	49	22·4	19·4	3·0
36–40	14	33·2	25·7	7·5	62	25·0	21·2	3·8

tions. Indian values are appreciably higher than the African.

A more detailed analysis has not been attempted since we are now taking part in a geographical survey of atheroma in the Americas, in association with Louisiana State University medical school and the Instituto de Nutrición de Centro America y Panama.

Discussion

The method of this survey shows the average severity of the disease more clearly than the conventional methods of simple separation into grades. It is open to criticism since a visual estimation of area is involved. Other workers, including Robertson (1959), have commented on the reproducibility of the method. It is advisable, however, if one is comparing racial groups, to have specimens from these groups included in the survey, and we suggest that the findings of Laurie and Woods (1958) differ from ours because they had no European or Indian cases with which to compare.

Higginson and Pepler (1954) concluded that severe aortic and coronary atherosclerosis are less common among Bantu patients in Johannesburg than in European and American populations. Sachs (1959) in Cape Town, comparing the European, African, and coloured populations, came to a similar conclusion. We do not believe that the African in Natal differs from the African in other parts of South Africa.

Our contention that aortic atheroma is more severe in the European is further supported by a comparison of the incidence of aneurysm of the abdominal aorta in the two races (table II). Syphilitic aneurysm—mainly of the arch and the thoracic aorta, but occasionally in the abdominal aorta—is still often found in the African. Abdominal aneurysm due to gross atheroma is extremely rare in the African, though common in the European. Indians are omitted because of insufficient numbers.

TABLE II—ABDOMINAL ANEURYSM DUE TO ATHEROSCLEROSIS IN EUROPEANS AND AFRICANS, 1950–59

Age-group	European	African
51–60	2 in 255 necropsies	*1 in 534 necropsies
61–70	12 in 381 „	0 in 293 „
71–80	15 in 334 „	0 in 135 „
Over 80	4 in 113 „	0 in 13 „

*Syphilis not excluded.

The present series shows the much-quoted low incidence of myocardial infarction in the African (table III). Cerebral softening does not seem to show the same low incidence. We are not certain, however, whether these cases are all thrombotic in origin. A survey of cerebral atheroma is now being undertaken. Cerebral hæmorrhage, in our opinion, is related to hypertension rather than to atherosclerosis.

While it is clear that factors other than atheroma may play a part in the development of myocardial infarction, this must not be allowed to obscure the fact that there are differences in severity of atheroma between African, European, and Indian. We do not accept the concept of Laurie et al. (1960) that the Bantu shows a different response from the European to atherosclerosis since, though gross myocardial infarction and sudden death is uncommon, minute infarcts occur which cause patchy fibrosis of the myocardium and resultant cardiac failure. Minute foci of ischæmic fibrosis, especially in hypertensive hearts, may not be related to atheroma of the coronary artery. Clinicians in King Edward VIII Hospital do not agree that angina pectoris is a frequent symptom in African patients. Unlike Laurie et al. (1960), we believe there is a form of cardiomyopathy in Africans which causes repeated attacks of congestive heart-failure, and which is not related to coronary-artery disease.

TABLE III—CARDIAC AND CEREBRAL VASCULAR DISEASE IN AFRICANS, EUROPEANS, AND INDIANS

Race	Myocardial infarction (recent and healed)	Cerebral softening	Cerebral hæmorrhage
	Cases	Cases	Cases
African	3 (0·9%)	12 (3·6%)	27 (8·1%)
European	12 (13·6%)	6 (6·8%)	2 (2·3%)
Indian	9 (9·1%)	5 (5·1%)	10 (10·3%)

I wish to thank Dr. G. G. Roach for collecting European material. This investigation was aided by a grant from the United States Public Health Administration.

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LYMPHADENOID GOITRE AND THE SYNDROME OF SYSTEMIC LUPUS ERYTHEMATOSUS

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IN lymphadenoid goitre (Hashimoto's disease), the granulomatous replacement of the thyroid, the presence of demonstrable antibodies in the blood, and the progressive clinical course into myxœdema are accounted for by the " leak hypothesis " (Roitt et al. 1956, White 1957), which envisages an escape of antigen(s) from the acini stimulating a cellular immune response in the body of the thyroid and regional lymph-nodes. The antigens are regarded as autoantigens, which in the normal subject are permanently segregated and thus are neither available at an early stage of development to provoke and sustain immunological tolerance nor able later to provoke antibody production. The cause of the initial " leak " of autoantigens is quite obscure at present, although tentative suggestions have been made that mumps and other virus infections may be responsible (Eylan et al. 1957).

Many authorities have drawn attention to lesions in organs other than the thyroid in Hashimoto's disease. Luxton and Cooke (1956) state that the liver and spleen may be abnormal, and Luxton (1957) has described associated Paget's disease. Wells (1930) described changes in the adrenals. Cardell and Gurling (1954) noted the resemblance between the histological appearances of the salivary and lacrimal glands in Sjögren's syndrome and the thyroid in Hashimoto's disease; and Heaton (1959) has suggested that Sjögren's disease and lymphadenoid goitre have causal factors in common. Since Heaton has produced extensive evidence that Sjögren's syndrome,

TABLE I—SEROLOGICAL FINDINGS IN 40 CASES OF LYMPHADENOID GOITRE

Precipitin test (agar-diffusion technique)	Positive (27)			Negative (13)		
Serum titres in hæmagglutination test (using formalinised-tanned sheep red cells sensitised with purified thyroglobulin)	5×10	5×10^2	5×10^3	5×10^4	5×10^5	5×10^6 and above
No. of sera	4	2	2	3	2	27
Serum titre in complement-fixation test	0	4–8	16–32	64–128	256–512	1024–2048
No. of sera	3	2	15	14	5	1

Mikulicz's disease, and Felty's syndrome are manifestations of systemic lupus, it is of some importance to explore the relation of Hashimoto's disease to other manifestations of systemic lupus. In an investigation (Christian and Dawson 1959) in which a preserved collection of sera from cases of lymphadenoid goitre was submitted to a lupus-erythematosus (L.E.) test with normal homologous leucocytes, all 20 sera tested gave negative results. One of us (White 1959) has described antinuclear serum factors in 4 out of 25 cases of lymphadenoid goitre. The present report gives clinical details of these four cases, and of one other which was found later.

The basis for this investigation has been 40 cases of lymphadenoid goitre, diagnosed clinically, and confirmed in most cases by the histological examination of the thyroid.

Material and Methods

Sera.—Fresh sera were stored frozen at −26°C before testing.

Fluorescein-conjugated antihuman γ-globulin.—Antisera were prepared in the rabbit by injection of purified γ-globulin, 2 mg. subcutaneously in Freund-type adjuvant mixture, followed by a recall injection six weeks later of 2 mg. γ-globulin adsorbed to 3·5 mg. aluminium phosphate. Antisera used for conjugates, absorbed if necessary, were tested by immunoelectrophoresis and were shown to give strong precipitin reactions with γ-globulin, and no apparent reaction with other electrophoretic serum components. Fluorescein conjugates were prepared by a modification of the method of Coons and Kaplan (1950), and were used after absorption twice with acetone-lyophilised mouse-liver powder (100 mg. per ml. serum).

Fluorescent antibody technique.—Thyroidectomy specimens were cut into small blocks, which were placed on the wall near the bottom of corked $6\times{}^5/_8$ in. 'Pyrex' test-tubes and quick-frozen in acetone-CO_2 mixture at −70°C. Frozen sections were cut at 5 μ thickness in a cryostat at −18°C, and were then thawed on clean slides and rapidly dried in a stream of warm dry air. After fixation in methanol for 15 minutes at room temperature, they were dried at 37°C for 30 minutes. After rehydration by a brief dip in buffered saline at pH 7·0, a drop of serum, which was either neat or diluted 1/5, 1/10, 1/20, and so on, was layered over the section in a moist atmosphere at room temperature. After 30 minutes, the section was washed in normal-saline buffer (pH 7·0) for 10 minutes, and then covered with a drop of fluorescein-labelled rabbit antihuman γ-globulin for 30 minutes, also at room temperature (20–22°C). Finally after a 10-minute wash in normal-saline buffer, the section was mounted in saline buffer for viewing under the fluorescence microscope. The source of ultraviolet radiation was a 20 amp. carbon arc, filtered through a glass cuvette containing 25% copper-sulphate solution and a 2 mm. glass filter (Corning 5840). A bireflecting dark-ground cardioid condenser was used. The eyepiece was provided with a gelatin 'Wratten' 2B filter.

Complement-fixation test.—The technique has not been published but is modified from that described by Bedson et al. (1949), employing a sensitised sheep-cell suspension of 2 (instead of 5) % and 2 minimum hæmolytic doses (M.H.D.) of guineapig complement. In addition, the mixtures of 0·1 amounts of serum dilution, complement, and antigen were not diluted with additional saline and the tubes were placed at 4°C for about 18 hours. After this they were brought to room temperature for 30 minutes, the cell suspension (0·2 ml.) was added, and the test was read after 30 minutes at 37°C in a water-bath, and again after 2–4 hours at room temperature. The antigen was a 25% w/v saline extract of fresh thyroidectomy thyroids. Control tissue antigens used in each test consisted of homologous brain, liver, lung, and suprarenal tissues, extracted under conditions identical with those used for the thyroid antigen and finally diluted to 25% (wet weight) in saline buffer pH 7·0.

Formalinised-tanned erythrocyte test.—Tanned sheep red cells were sensitised by exposure to purified human thyroglobulin (Derrien et al. 1948) and treated with formalin according to the technique of Fulthorpe (1957). A control series of serum dilutions was set up against unsensitised tanned-formalinised cells to determine the possible influence of Forssman antibody in the human sera. The highest dilution used in the test was 1/5 million at a final volume of 1 ml.

Results

The sera of 5 patients out of a total of 40 cases of lymphadenoid goitre were positive when tested for the presence of antinuclear factor. Briefly the test described above uses a frozen section (methanol-fixed) of normal thyroid tissue which is exposed first, to neat or 1/5 dilution of the patient's serum, and second, to fluorescein-conjugated rabbit antihuman γ-globulin.

The sera were derived from various sources, but came in the main from surgical thyroid clinics. In 28 of the 40 cases the diagnosis of lymphadenoid goitre was confirmed by histological examination of the gland.

Negative controls consisted of 30 sera from an antenatal clinic collected from mothers for serological tests for syphilis. Sera giving positive Wassermann, treponema-immobilisation, or Kahn-flocculation tests were excluded. Further controls consisted of 30 sera from routine blood-donors of both sexes. None of these sera gave nuclear fluorescence under the conditions of the test described here. Standardisation of time and temperature were found to be of importance; for, by exposing sera from these control groups overnight at 4°C, a high proportion yielded bright nuclear fluorescence. Positive controls for the standard test were from some cases of systemic lupus erythematosus which yielded consistently positive results.

Serological data from these 40 cases are included in table I. The complement-fixation test in 100 controls (antenatal patients) were with one exception all negative.

The cases yielding sera containing antinuclear factor by this fluorescent-antibody double-layer technique were as follows:

Case 1.—A woman, now aged 82, had noticed a lump in the right side of her neck for 20 years. She sought advice in November, 1956, because for two months the lump had been increasing in size. She had myxœdema, the thyroid was grossly enlarged, especially the right lobe ($1^1/_2\times1^1/_2$ in.) which was firm, smooth, and nodular, moving freely on swallowing. Plasma-proteins 8·8 g. per 100 ml. (globulin 4·3 g. per 100 ml.). Bilirubin 0·2 mg. per 100 ml.

TABLE II—SEROLOGICAL FINDINGS IN CASE 1

—	Dec., 1956	May, 1957	Jan., 1958	Apr., 1958	July, 1958	Sept., 1959
Complement fixation: serum titre for complete fixation of 2 M.H.D. dose of guineapig complement with saline extract of thyroid	32	64	64	32	32	16
Precipitin: agar-diffusion technique	+	+	+	+	+	+
Hæmagglutination of formalinised-tanned sheep red cells sensitised with purified thyroglobulin	$>5\times10^6$	$>5\times10^6$	$>5\times10^6$	$>5\times10^6$	$>5\times10^6$	$>5\times10^6$
Antinuclear factor: double-layer fluorescent-antibody technique on homologous thyroid section. Serum diluted 1/5	+	+	+	+	+	+

M.H.D. = minimum hæmolytic dose.

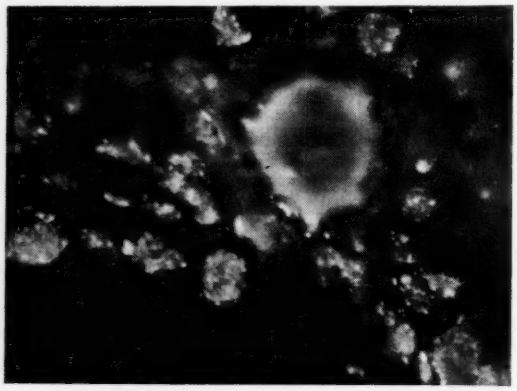

Fig. 1—Fluorescence micrograph of fluorescent-antibody test with serum of case 1. (×1080.)

Bright areas represent the sites of localisation of fluorescein-antibody conjugate in a frozen section of human thyroid, treated by the double-layer technique for nuclear antibody. The fluorescence is confined to nuclei of the follicular epithelium because of the presence of nuclear antibody in the serum of case 1. The γ-globulin within one vessel is also shown.

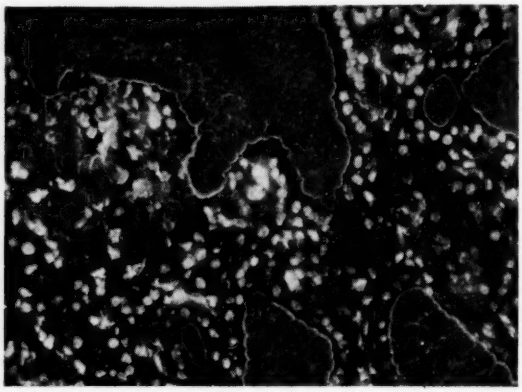

Fig. 2—Fluorescence micrograph of fluorescent-antibody test with serum of case 2. (×230.)

Double-layer technique for nuclear antibody. Section of human thyroid. The fluorescence is confined to nuclei of the follicular epithelium because of nuclear antibody in the serum of this case, and to the intrafollicular colloid (owing to an antibody, also in this patient's serum, presumably against thyroglobulin).

At operation a firm thyroid was partially removed. Histologically, the thyroid tissue was grossly disorganised by broad bands of dense fibrous tissue containing isolated groups of mature and immature plasma-cells. Areas of lymphoid cells contained well-developed germinal centres and peripheral areas of confluent plasma-cells. Acini of greatly diminished size were separated into small groups by the bands of fibrous tissue. Many contained a little, deeply eosinophilic colloid. Others were disorganised to multinucleate cellular masses. Many acinar cells showed bulky opaque eosinophilic cytoplasm (Askanazy-type degeneration).

Since her thyroidectomy, the patient has remained well. The serological findings during her illness are shown in table II. It is noteworthy that nuclear antibody (fig. 1) was first observed in November, 1956, at which time her serum gave a brilliant reaction in the fluorescent-antibody test even after dilution 1/60. She was then 78 years old and neither subsequently or at any time in the past has she shown any other indication of systemic lupus. Attempts to produce the L.E. phenomenon in vitro with her serum and normal leucocytes gave negative results (table II).

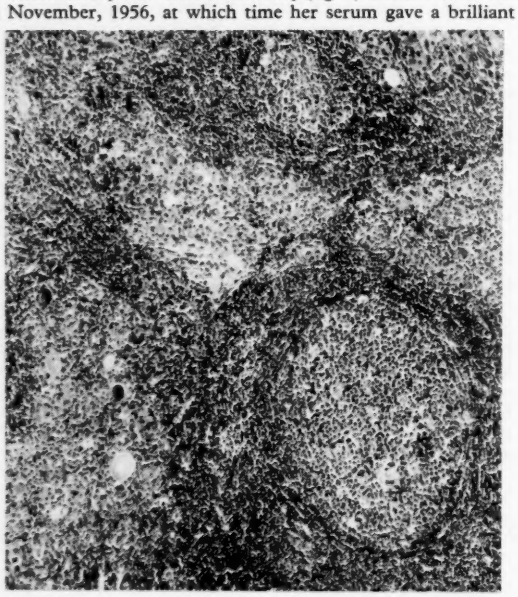

Fig. 3—Paraffin section of thyroid of case 2. (Hæmatoxylin and eosin. ×75.)

Note the two large lymphoid nodules with pale centres, and the irregular islands of small thyroid follicles separated by broad strands of lymphoid cellular infiltration.

Case 2.—A woman, now aged 55 years, was first found to have antinuclear factor in her serum by the fluorescent-antibody technique (fig. 2) in July, 1957. At this time she complained that a lump in the neck was causing dysphagia.

Plasma-proteins were 8·6 g. (globulins 4·7 g.) per 100 ml. The serum-precipitin test (agar-diffusion technique) with purified thyroglobulin was positive. Hæmagglutination of formalinised-tanned sheep red cells was positive to a serum dilution of 1/5 million. A complement-fixation test with a saline extract of normal homologous thyroid gave complete fixation to a serum dilution of 1/120. Partial thyroidectomy was done in July, 1957.

Histological examination of the removed thyroid (weight 33 g.) showed a diffuse infiltration with lymphoid cells. The thyroid acini were small and were separated by narrow columns of lymphoid cells, a high proportion of which were typical mature and immature plasma-cells. Scattered larger foci of lymphoid tissue were present and contained typical germinal centres. The acini, especially those in relation to the lymphoid cellular masses, were often disorganised sometimes severely (figs. 3 and 4). Acini containing colloidophages and eosinophil leucocytes were present. In a few places further acinar disorganisation had resulted in syncytial multinucleate masses. Pyknosis and irregularity of size and shape of acinar cell nuclei were apparent, as also was Askanazy degeneration in the acinar cells.

In 1950 she had had ulcerative colitis, which responded well to treatment.

She remained well until August, 1959, when she was again admitted. Her complaint was of general malaise and joint pains, affecting mainly the small joints of the hands and feet. She was miserable, icteric, and febrile (99·6°F). The liver was firmly enlarged, and palpable 3 fingers-breadth below the costal margin. The erythrocyte-sedimentation rate (E.S.R.) was 125 mm. in the first hour (Westergren), and the blood showed leucocytosis of 20,600 cells per c.mm. (56% polymorphonuclear neutrophils). The plasma-proteins were 9·7 g. (globulins 6·6 g.) per 100 ml. and plasma electrophoresis showed a very high level of γ-globulin. Liver-function tests gave a serum-bilirubin content of 2·5 mg. per 100 ml., alkaline phosphatase 53 King-Armstrong (K.A.) units, thymol turbidity 19 units, and zinc-sulphate turbidity 40 units.

TABLE III—SEROLOGICAL FINDINGS IN CASE 2.

—	July, 1957	Sept., 1957	Jan., 1958	Aug., 1958	Aug., 1959	Sept., 1959
Complement fixation: serum titre for complete fixation of 2 M.H.D. dose of guineapig complement with saline-thyroid antigen-extract	120	150	180	180	180	..
Precipitin test: agar-diffusion technique	+	+	..	..	..	..
Hæmagglutination of formalinised-tanned sheep red cells sensitised with purified thyroglobulin	$>5\times10^6$	$>5\times10^6$	..	..	5×10^5	5×10^6
Serum antinuclear factor: double-layer fluorescent-antibody technique on homologous thyroid section. Serum diluted 1/5 ..	+	+	+	..	+	+

Numerous L.E. cells were seen in preparations of the peripheral blood. The serum at dilution 1/5 produced bright nuclear reaction in the fluorescence-antibody technique on sections of normal homologous thyroids. Hepatic biopsy material showed scattered periportal foci of lymphocytes and plasma-cells, reported to be consistent with a diagnosis of lupoid hepatitis.

During admission she had a transient left pleural effusion with pericarditis.

Steroid hormones, however, produced a dramatic clinical improvement. The E.S.R. (Westergren) fell to 30 mm. in the first hour, but the plasma-protein level remained high (9·3 g., globulin 5·9 g. per 100 ml.). Thymol turbidity was 16 units, zinc-sulphate flocculation 24 units, and alkaline phosphatase 60 K.A. units.

The further course of the serological findings are shown in table III. Controls used in each complement fixation consisted of homologous brain, liver, lung, and suprarenal tissues. Fixation of complement of the 2 M.H.D. complement dose was either absent or minimal by such control tissue suspensions.

An incidental finding was the presence of many Howell-Jolly bodies in the patient's erythrocytes. The possibility was considered that these, which were Feulgen-positive, represented the result of an interaction of desoxyribose nucleic acid and serum nuclear antibody. Fresh methanol-fixed blood-smears exposed to rabbit antihuman γ-globulin failed, however, to show the presence of globulin in these bodies. The direct and indirect Coombs tests were negative.

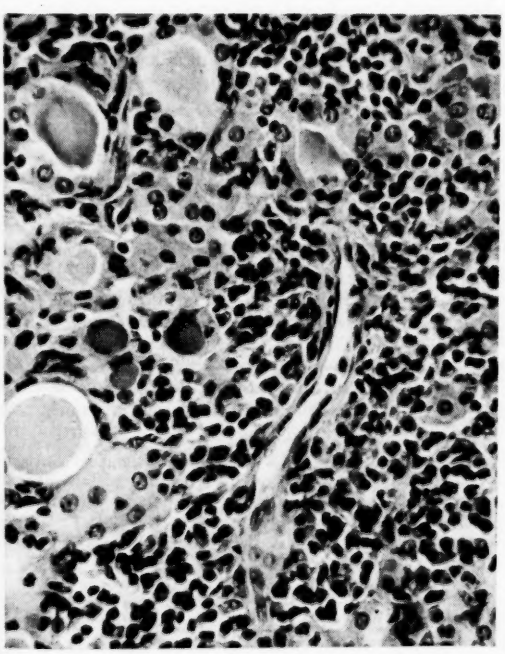

Fig. 4—Higher power view of thyroid of fig. 3 (case 2). (H. & E. ×290.)

Note dense perivascular infiltration of plasma-cells in close relation to small, somewhat disorganised, colloid-containing, and in places empty thyroid acini.

Case 3.—A woman, aged 48, was admitted on July 23, 1956, with a refractory anæmia of 3 months' duration. Apart from pallor, there were no abnormal signs. The thyroid was not enlarged and though her doctor had considered the possibility of hypothyroidism there was no confirmation of this and the results of investigations, including measurement of blood-cholesterol, electrocardiography, and determination of basal metabolic-rate were normal.

Before admission her hæmoglobin was 9·4 g. per 100 ml., red-cell count 2·6 million per c.mm. (reticulocytes 12%). On July 25, the E.S.R. (Westergren) was 130 mm. in the first hour. Sternal marrow examination (Aug. 3) showed normoblast hyperplasia, but the reticulocyte-count had now returned to normal.

The diagnosis of hæmolytic anæmia was supported by a direct Coombs test and a trace of a nonspecific incomplete antibody was shown by an indirect Coombs test done at 37°C.

Prednisone was given during the succeeding $4^1/_2$ months.

In March, 1958, the patient suddenly became ill with shivering and nausea. During the next week she was feverish and vomited frequently; a generalised purpuric eruption appeared. She then attended hospital with severe episcleritis of the right eye. This responded to oral prednisolone but later returned mildly in both eyes while she was still taking the drug.

In May, 1958, slight diffuse thyroid enlargement was noted, and again 6 months later. She was not obviously hypothyroid. Serum-proteins were 8·7 g. (globulin 4·1 g.) per 100 ml., and the serum colloidal-gold reaction was strongly positive. The thymol turbidity was raised to 16·0 units, and the zinc-sulphate flocculation to 15·5 units. Alkaline phosphatase in the serum was 9·75 K.A. units, and serum-bilirubin was 0·4 mg. per 100 ml. A serum complement-fixation test using antigen of thyroid tissue showed complete fixation of 2 M.H.D. of complement to a serum dilution of 1/128 (January, 1959). A later serum titre (October, 1959) was 1/32. Precipitin test by the agar-diffusion technique was negative. Hæmagglutination of tanned-formalinised sheep red cells gave a titre of 1/50 (January, 1959) and 1/500 (October, 1959).

A needle biopsy of the thyroid was unsuccessful, and the diagnosis of lymphadenoid thyroiditis was not confirmed by histological examination in this patient.

In January, 1959, a test for nuclear antibody by the fluorescent-antibody technique on a frozen section of thyroid tissue was positive. The test was still positive in October, 1959. Attempts to obtain an L.E.-cell phenomenon with the patient's whole blood were unsuccessful.

Case 4.—A woman, aged 58, was admitted in July, 1958, after a 2-year history of general abdominal pain, increasing tiredness, palpitations, and a loss of 14 lb. over the preceding 6 months. Her thyroid gland was diffusely enlarged and firm. Her pulse-rate was 132 per minute. Iodine uptake was 56% in 24 hours. Complement-fixation tests with an aqueous extract of human thyroid tissue gave complete fixation at serum titres of 1/32 (June, 1958), 1/32 (November, 1959). Hæmagglutination test with formalinised-tanned erythrocytes sensitised with purified thyroglobulin gave agglutination to a serum titre of 1/50 (November, 1959).

A subtotal thyroidectomy was performed. Section of this gland showed a focal epithelial hyperplasia consistent with thyrotoxicosis. The section was diffusely permeated by narrow

TABLE IV—CLINICAL FINDINGS IN LYMPHADENOID GOITRE WITH ANTINUCLEAR SERUM FACTOR

Case no.	Sex	Age	Clinical findings
1	F	78	Rheumatic fever in childhood
2	F	58	Ulcerative colitis; systemic lupus erythematosus, with lupoid hepatitis; pericarditis; pleural involvement; and polyarthritis
3	F	48	Hæmolytic anæmia, purpura, and episcleritis
4	F	55	Nil
5	F	49	Rheumatoid arthritis, chronic rheumatic carditis

strands of lymphoid tissue containing leucocytes and plasma-cells, with an occasional lymphoid nodule with germinal centre. Near the edge of such lymphoid strands were multinucleate islands of disorganised thyroid epithelial cells. The same areas showed Askanazy-type changes in the thyroid epithelial cells.

Fluorescent-antibody test for serum antinuclear factor were positive with neat and with 1/10 serum dilutions.

Case 5.—A woman, now aged 49, was first seen in October, 1959, complaining of pain, stiffness, and swelling in the hands and feet for 18 months. Her left shoulder, knees, elbows, and neck had all been involved. She was obviously myxœdematous, and the thyroid was moderately enlarged and firm. In addition to a moderately severe active rheumatoid arthritis she showed the signs of chronic rheumatic carditis—in the form of mitral stenosis and atrial fibrillation. The myxœdema disappeared on treatment with thyroid, and the goitre diminished.

The hæmagglutination test with formalinised-tanned erythrocytes sensitised with thyroglobulin gave agglutination to a serum dilution of 1/500,000. The complement-fixation test with an aqueous extract of thyroid tissue was negative at 1/8 serum dilution.

The latex-particle test (technique of Singer and Plotz 1956) gave agglutination to a serum titre of 1/640.

White cells 4400 per c.mm., hæmoglobin 11·5 g. per 100 ml. The direct Coombs test was negative. No L.E. cells were seen in preparations of the patient's defibrinated blood. A histological report on thyroid tissue was not available.

Table IV summarises the clinical findings in these 5 cases.

Discussion

These investigations are relevant to current hypotheses about the formation of lymphadenoid goitre, which may be regarded as a disease caused by local events in the thyroid gland. Presumably the escape of segregated antigens starts an immune response which damages the gland, leading to further " leak " of antigens, and to the progressive replacement of the acinar thyroid tissue by a granuloma of histiocytes, plasma-cells, and nodular arrangements of lymphocytes.

The association of lymphadenoid goitre with other diseases of " autoallergy "—e.g., hæmolytic anæmia (Wasastjerna 1959), Addison's disease (Anderson et al. 1957), Paget's disease of bone (Luxton 1957), hepatitis (Luxton and Cooke 1956), and systemic lupus erythematosus—raises the question of the adequacy of the " leak " hypothesis, unless, of course, such additional manifestations of disease can be accounted for by coincidence. Indeed, Heaton (1959) inferred from the similarity of the histological picture in Hashimoto's disease and Sjögren's syndrome, that both may be a manifestation of systemic lupus erythematosus.

Christian and Dawson (1959) investigated this by testing sera from 20 cases of lymphadenoid goitre for their ability to induce the L.E. phenomenon with normal homologous leucocytes. In no case was a positive result obtained. It is often difficult, however, particularly with stored sera, to elicit the L.E.-cell phenomenon in vitro.

The double-layer fluorescent-antibody technique for detection of serum antinuclear factors, as used in this investigation, is regarded as a sensitive indicator of systemic lupus erythematosus. Several investigators have reported that similar tests are positive in a high proportion of cases of systemic lupus (Friou 1958); and in this investigation 22 of the sera from 27 cases of systemic lupus were strongly positive by this technique.

The finding of only 5 positive sera out of 40 sera from cases of lymphadenoid goitre is not regarded as support for the hypothesis that lymphadenoid goitre is a direct manifestation of systemic lupus erythematosus. Rather, as previously argued by White (1959), such findings may indicate that there is a small subgroup of cases of lymphadenoid goitre which have arisen in patients (with systemic lupus) who have a special propensity to form antibodies generally. Thus the possessors of this trait may respond with antibody production and with immune cellular infiltration of the thyroid to amounts of escaping antigens which are tolerated by normal subjects. Callender and Race (1946) have described how antibodies to the weak erythrocyte antigens c and N and to other previously undescribed antigens may occur in such patients. The occurrence of a hæmolytic anæmia (with positive direct and indirect Coombs tests) in case 3, as also in the case described by Wasastjerna (1959) is of interest. Cases of systemic lupus are well-known sources of biological false-positive reactions in the Wassermann test, and their serum often contains cold agglutinins (Gold and Gowing 1953).

The existence of such a subgroup of lymphadenoid goitre associated with the syndrome of lupus erythematosus may partly explain the association of hepatitis with lymphadenoid goitre (Luxton and Cooke 1956), for such cases may prove to be lupoid hepatitis (Mackay et al. 1956).

The view is sometimes put forward that autoantibodies represent the consequence of, rather than the initiating factors in, disease processes. In case 2, it is, therefore, interesting that the presence of nuclear antibody in the serum preceded by 2 years the appearance of severe clinical manifestations of systemic lupus erythematosus.

Summary

40 cases of lymphadenoid goitre (Hashimoto's disease) were tested for the presence in the serum of antinuclear factor, using a histological technique with fluorescent antibody. 5 cases were positive. In 2 patients no other disease was present. 1 patient had signs of systemic lupus erythematosus 2 years after a positive serum reaction for antinuclear factor, and in another the findings also suggested this diagnosis. In the 5th case, rheumatoid arthritis and rheumatic carditis were present. The existence of such a subgroup of cases of lymphadenoid goitre is discussed in relation to the " leak " hypothesis of the pathogenesis of this disease.

We are indebted to Mr. W. H. Kingham for technical assistance. The serological control data relating to cases of lymphadenoid goitre and normals are extracted from an investigation undertaken in collaboration with Prof. C. F. Barwell and Mr. W. F. P. Gammie which is to be published.

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Addendum

Since this paper was written, E. J. Holborow (*Proc. R. Soc. Med.* 1960, **53**, 625) reported an investigation in which the sera of patients with systemic lupus erythematosus were tested for a globulin with an affinity for cell nuclei. Holborow concluded that the L.E.-cell factor and the antinuclear factor were separate.

CHRONIC RINGWORM OF THE NAILS

Long-term Treatment with Griseofulvin

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SINCE griseofulvin was first used in the treatment of human ringworm infections by Riehl (1958), Williams et al. (1958), and Blank and Roth (1959), the favourable results in these preliminary trials have been confirmed by subsequent investigators using the drug in the treatment of many, but not all, types of fungous infections.

Trichophyton rubrum is responsible for the most intractable form of ringworm of the skin and nails. Spontaneous remissions in this type of infection are rare. A therapeutic trial of griseofulvin in chronic ringworm of the skin and nails was reported by Russell et al. (1960). From this and other published reports it was evident that griseofulvin is effective in the treatment of *T. rubrum* infection of the skin with exception of the toe-webs, where infection tended to persist despite lengthy treatment.

Treatment of onychomycosis of the fingers was successful in a high proportion of cases, provided that treatment was prolonged for several months. We have followed up patients who took part in this trial and the results were: 41 patients with fingernail infection were reviewed one year after starting treatment with griseofulvin. 34 patients grew normal nails in which no fungus was found on direct examination, this result being achieved in eight months or less in 28 cases. 4 more patients were apparently cured of fungus, as detected microscopically, but dystrophy persisted owing, in 2 patients, to an intercurrent monilial infection. 3 patients, 1 with hyperhidrosis, had abnormal nails in which fungus was still found after a year's treatment.

The results of treatment of toenail infections with griseofulvin have been less promising, according to reports from Russell et al. (1960), Williams (1960), and others; but, in view of the slow growth of toenails, lengthy treatment would be required before a final verdict could be given. Long-term treatment with griseofulvin has been reported in several small series—for example, by Hargreaves (1960), who compares the results of such treatment, given alone, with a combination of avulsion of the nails and griseofulvin therapy. The latter method has been reported by Reisner et al. (1960), but they compare their results with those of treatment with griseofulvin alone, given for variable periods (all less than one year), and in variable dosage. A report on a large series of cases of onychomycosis of the toes would give a clearer picture of the effect of long-term griseofulvin therapy alone, and would be useful for comparison with any published results of treatment by avulsion combined with griseofulvin. Another problem was the persistence of fungus in the toe-webs even after long periods of therapy; this also has been studied in the present investigation.

Method

50 patients with chronic *T. rubrum* infection of the toenails and skin of the feet were studied: some patients also had fingernail infections. All but 2 patients, both of whom had gross toenail dystrophy, had noticed lesions for at least two years; and, in over half the patients, the period was more than ten years. The 50 patients were aged between 16 and 69: 26 were males. Griseofulvin was given in a dose of 0·5 g. thrice daily for one year, unless microscopical examination of the previously affected toenails, fingernails, toe-webs, and any suspicious areas on the soles of the feet was negative on two consecutive occasions at an interval of one month. At the second examination cultures were also made. If these tests of cure were negative, treatment was stopped and monthly follow-up examinations for fungus by direct and cultural methods were continued.

In 14 of the patients in whom the infection persisted after one year, treatment was continued uninterrupted to a total period of fifteen months and the results were reassessed.

Results

Response to Treatment

Of 50 patients with toenail infections, 38 received one year's treatment; 12 others were cleared of fungus before one year had elapsed and treatment was stopped after seven to eleven months. All patients were reviewed at the end of one year (table I).

In 30 patients fungus was present in the toenails after a year's treatment and, in 13 of these, the skin of the toe-webs or soles of the feet was still infected. In addition, 4 patients with no fungus in the nails still had fungus in the skin; but, in 1 of them, the fungus grown was *T. mentagrophytes* var. *interdigitale* (= *T. interdigitale* Priestley). All the other positive cultures obtained at one year were *T. rubrum*. Out of 50 patients, therefore, only 16 were clear of fungus at all sites by the end of one year.

In 14 patients (table II) in whom infection persisted at one year, treatment was prolonged for a further three months. This resulted in clearance at all sites in 5 patients.

Follow-up of "Cured" Cases

Table III shows that, of 21 patients cleared of fungus at all sites, a recurrence of fungus was found in the nails within three months in 5, and in the skin in a further 8. In 1 patient a different fungus (*T. mentagrophytes* var. *interdigitale*) was grown from a toe-web.

TABLE I—*Trichophyton rubrum* INFECTION OF TOENAILS TREATED WITH GRISEOFULVIN FOR UP TO 1 YEAR

—	Number	Remarks
Patients treated until cured, or for a minimum of one year	50	..
Patients shown to harbour fungus at the end of one year	34	Fungus in toenails only 17 " " " +skin 13 " " skin (toe-webs or soles only) 4*
Cured—no fungus at any site at end of one year	16	..

* In one case *T. mentagrophytes* var. *interdigitale* was grown from toe-web.

TABLE II—*T. rubrum* INFECTION OF TOENAILS TREATED CONTINUOUSLY FOR 15 MONTHS

—	Number	Remarks
Patients treated for 15 months	14	..
Patients harbouring fungus at end of 15 months	9	Fungus in toenails only 5 " " " +skin 3 " " skin only 1
Patients without fungus at any site at end of 15 months	5	..

Cultural Studies

In all 50 patients the fungus was identified as *T. rubrum* before treatment was begun. At the end of one year all culture examinations were repeated, and yielded *T. rubrum* in 23 cases, *T. mentagrophytes* var. *interdigitale* in 1 patient (from skin), and negative results in 26. Cultures on " cured " patients who relapsed yielded *T. rubrum* in 6, *T. mentagrophytes* var. *interdigitale* in 1 (from skin), and were negative in 5 patients. Monilial infection took place in some patients with gross nail dystrophy.

Sensitivity Tests and Serum-griseofulvin Levels

In-vitro sensitivity tests to griseofulvin by the double-dilution method were carried out on cultures from 6 patients who had responded poorly to griseofulvin, but there was no evidence of diminished sensitivity to the drug. The level of griseofulvin in blood was estimated (method of Muggleton and Marshall, unpublished) in 36 patients (27 of whom were " failed " cases at the end of one year). In all samples of blood taken, griseofulvin was present in the serum at a level of 2°5–7°5 μg. per ml.

TABLE III—FOLLOW-UP OF PATIENTS CLEARED OF TOENAIL INFECTION

—	Number	Remarks
Patients cleared 1 year after starting treatment	16	..
Patients cleared 15 months after starting treatment	5	..
Total ..	21	..
3-months minimum follow-up—no fungus at any site	8	..
Relapsed—fungus present	13	Fungus in toenails 5 " " skin only 8*

* In one case *T. mentagrophytes* var. *interdigitale* was grown from toe-web.

Discussion

Of our 41 patients with onychomycosis of the fingers, only 3 still showed infection after treatment for one year (28 being cleared of fungus within eight months). We have yet to see a relapse in a " cured " fingernail.

The disappointing results with toenail infections may be due to various factors. In-vitro resistance of *T. rubrum* to griseofulvin has not been reported and was not shown by 6 patients studied in this series. The finding of griseofulvin in all samples of blood taken from 36 patients under treatment at least suggests that patients were taking their griseofulvin regularly. That nails grow more slowly on the feet than on the hands is well recognised, and the figures given by Edwards and Schott (1937) indicate that fingernails grow twice as fast as toenails. On this basis, one would expect to require a longer period of treatment to eradicate infection from the toenails. We do not, however, believe that this factor accounts wholly for the poor results of treatment prolonged for a year, or even fifteen months. Perhaps excessive sweating and humidity within footwear is important.

Undeniably, the high relapse-rate of " cured " cases could be due to reinfection from footwear or bath-mats, but the difficulty in clearing the infection from the toe-webs seems to be a more important factor.

Summary and Conclusion

Treatment with griseofulvin by mouth for one year—unless the infection was cleared sooner—was given to 50 patients with chronic onychomycosis of the feet due to *Trichophyton rubrum*. The nails were cleared of infection in 20 patients, but 4 of them still had fungus in the toe-webs.

After fifteen months' treatment of 14 patients with toenail infection, 8 still had fungus in the nails and 1 in the skin only.

Of 21 patients cleared of fungus (toenails and skin), fungus was found in one or other of these sites in 13 cases within three months of stopping treatment.

By contrast, in 38 of 41 patients in the same trial, the fingernails were cleared of infection within one year of starting treatment, and there was no relapse at this site.

The long-term treatment of onychomycosis of the feet with griseofulvin alone appears unsatisfactory in a high proportion of cases. A combination of avulsion of the nails and griseofulvin may prove to be the best treatment provided that persistent toe-web infection can be overcome.

We are grateful to Dr. R. W. Riddell and to Dr. Brian Russell for their encouragement and advice, and to the physicians to St. John's Hospital for Diseases of the Skin, London, for referring patients to us.

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CONGENITAL FIBROSIS OF THE LIVER AS A FAMILIAL DEFECT *

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CONGENITAL cystic disease of the liver is well recognised. A variant of the condition known as congenital fibrosis of the liver is now being recognised more often (Parker 1956, Harrison et al. 1959). In congenital fibrosis of the liver there is an excess of small bileducts which show no cystic dilatation. The fibrosis predominates in the portal tracts, the zonal pattern being otherwise normal. There may be an associated congenital cystic disease of the kidneys (Melnick 1955, Parker 1956, Sherlock 1958), and of the pancreas (Ivemark et al. 1959). The present study concerns three siblings, all affected.

Case-reports

Case 1.—A boy, now aged 11, was first seen at the age of 2 with an enlarged abdomen. He was of average weight and height, with a firm uniformly enlarged liver, extending 3–4 in. below the costal margin. The spleen was palpable. There was no previous medical or family history of significance. The mother and father were only children. Investigations revealed a normal blood-picture. The Wassermann, Kahn, and Mantoux tests were negative. Urinary examination showed a few epithelial cells only; no proteinuria. An intravenous

* Paper presented at a meeting of the Swedish Pædiatric Association, Stockholm, on Sept. 28, 1960.

pyelogram showed that both kidneys excreted well and their structure appeared normal. The serum-electrolytes were normal. Specific liver investigations showed: prothrombin-time 14 seconds (40–50%), bilirubin 0·4 mg. per 100 ml., thymol turbidity 7 units, alkaline phosphatase 8 King-Armstrong units, total proteins 8 g. per 100 ml. (albumin 4·5 g., globulin 3·5 g.). The glucose-tolerance test was normal. There was no evidence of Rh or other blood-group incompatibility between mother and child.

Laparotomy confirmed that the liver was large and of uniform hard consistence. The spleen was enlarged and firm. The kidneys were of normal size. Biopsy of the liver showed the typical changes of congenital fibrosis.

The boy remained well until 2 years later when he had a large hæmatemesis, which ceased after a transfusion of 2 pints of blood. There was no appreciable change in the size of the liver. The spleen was enlarged, extending 4–5 in. below the costal margin. A barium swallow showed varices in the lower part of the œsophagus; later confirmed by œsophagoscopy. Hæmorrhoids were seen on proctoscopy. A splenogram (fig. 1) showed normal splenic and portal veins with gastro-œsophageal varices extending to the aortic arch. In September, 1954, at the age of 5, he had a side-to-side portocaval anastomosis carried out by Mr. G. H. Wooler. The portal-vein

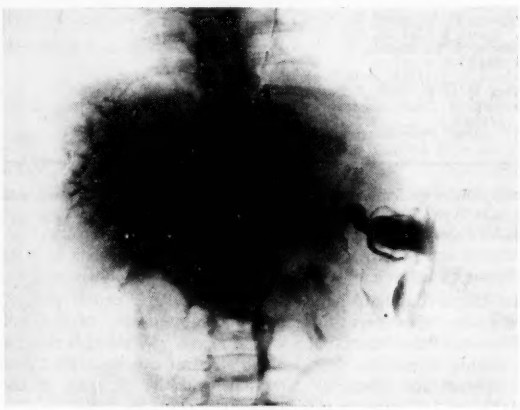

Fig. 1—Splenogram of case 1.

pressure before the anastomosis was 60 cm. of water and the pressure in the inferior vena cava, 1·6 cm. of water. A post-operative splenogram showed that the collaterals no longer filled.

6 years later, at the age of 11, the boy is well, of normal height and weight, attends school regularly, and takes part in all activities. The spleen has gradually decreased in size and is no longer palpable. He now has numerous spider nævi. There is no change in the size of the liver. The numerous liver investigations all remain essentially normal. Repeated urine analysis shows no abnormality. Blood-urea remains 30–40 mg. per 100 ml. He can concentrate urine to 1·020. Blood-pressure is 95/65 mm. Hg. Further intravenous pyelography, done as a result of the findings in the youngest sibling (case 3), shows that he has cystic kidneys.

Case 2.—A girl, now aged $12^1/_2$, the eldest of the three siblings, was admitted at the age of 5 with a hæmatemesis. She was a well-nourished child of average weight and height with a large abdomen due to an enlarged liver of firm uniform consistence and to an enlarged spleen. The bleeding ceased after a transfusion of 2 pints of blood. There was no significant previous history. A series of liver-function tests, similar to those of case 1, were carried out—again with normal results. A barium swallow showed the presence of œsophageal varices, confirmed by œsophagoscopy. A splenogram (fig. 2) showed patent splenic and portal veins and an enlarged left gastric vein arising from the portal vein and gastroœsophageal varices. Hepatic-vein catheterisation showed a pressure of +28 cm. water.

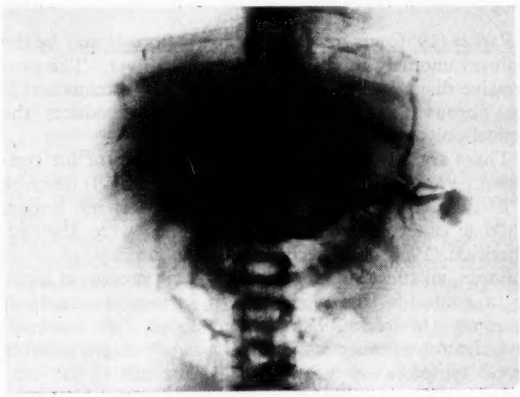

Fig. 2—Splenogram of case 2.

Early in 1954, when she was 6, a side-to-side portocaval anastomosis had been performed by Mr. Wooler. The liver was found to be large, and of firm even consistence. The gall-bladder was greatly distended, without obvious disease in it or in the bileducts. A biopsy showed the typical changes of congenital fibrosis.

She has remained well since. Repeated liver-function tests have failed to show any significant abnormality. Urine analysis remains normal, and an intravenous pyelogram shows normal excretion and outline.

The mother raised the question of a further pregnancy. In the light of our knowledge at the time (1954), and after exhaustive inquiries, the only rational explanation for the familial pattern of the disease seemed to be that the two children had been infected with a hepatitis virus, probably from a common source—probably a close member of the family.

Case 3.—A third child, a girl, was born in January, 1955. The baby was seen regularly and at 6 months appeared a normal thriving infant. A month later she was admitted with persistent vomiting and pyrexia. She was found to have pyelitis. Her liver was palpable 2 in. below the costal margin. The spleen was not felt. She responded initially to treatment, but relapsed and died a month later of septicæmia. A postmortem examination showed generalised pyæmia, originating in bilateral pyelonephritis. The liver was uniformly enlarged, weighing 1 kg. Macroscopically there were no œsophageal varices. Histological examination revealed the typical changes of hepatic fibrosis (fig. 3) and cystic disease of the kidney. The pancreas was found to be normal. Because of the kidney findings, the other two children were re-examined; and, although neither had symptoms referable to the urinary system, the boy was found to have cystic kidneys.

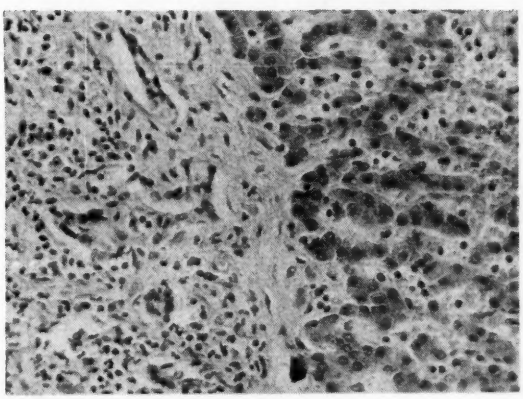

Fig. 3—Case 3. Hepatic fibrosis. (×150.)

Discussion

Parker (1956) suggested that hepatic fibrosis may be the primary anomaly in cystic disease of the liver. The progressive dilatation of the bileducts and the attenuation of the fibrous tissue which develops later produces the typical polycystic liver.

There are few reports of familial instances of the condition. Parker (1956) and Ivemark et al. (1959) describe it in two siblings in two families, but it is not known whether other members of the families were affected. Sherlock (1960) has records of two families of three children, all affected. The condition may present at birth, or in adult life, or it may be an incidental finding at necropsy (Melnick 1955, Parker 1956). A thorough investigation of other members of a family might possibly reveal symptomless cases. The occurrence of the condition in all three children in three families would suggest that congenital fibrosis of the liver is genetically determined and may well be dominant.

In the youngest (case 3), the cause of death was pyelonephritis superimposed on congenital cystic kidneys which are often associated with congenital fibrosis of the liver. The presenting feature in case 1 was hepatosplenomegaly followed by hæmatemesis; in case 2 hæmatemesis was the presenting symptom. Both patients were protected from further hæmorrhage from œsophageal varices by successfully anastomosing the high-pressure portal vein to the low-pressure inferior vena cava. The children have remained well after follow-up periods of $6^1/_2$ and 6 years, and show a normal gain of height and weight. There have been no obvious neuropsychiatric complications. This is interesting because a large proportion of their portal blood must be diverted directly into the systemic venous system. Routine laboratory investigations have shown no impairment of liver function.

Summary

Congenital hepatic fibrosis in three siblings is reported.

One developed renal failure in the 1st year of life. Necropsy showed hepatic fibrosis and congenital cystic kidneys.

The other two remain well, 6 years later, having had portocaval anastomoses carried out for hæmatemesis. One child has congenital cystic kidneys.

Congenital hepatic fibrosis may be a genetically determined defect, and is probably dominant.

We are greatly indebted to Mr. G. H. Wooler for the surgical care of cases 1 and 2, and for his subsequent interest and help. Our thanks are due to Prof. Sheila Sherlock and Dr. David Kerr for advice, and to Dr. A. J. E. Barlow for the photomicrographs.

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New Inventions

THE COLPORRHAPHEUR

A New Instrument for Treating Stress Incontinence

IN my experience some degree of stress incontinence is found in 75% of multiparous women over the age of 40, but no satisfactory way of treating it has yet been evolved,[1 2] and recurrence of the symptoms after operation is common.[3] To facilitate plication and invagination of the pubocervical fascia, I have devised the colporrhapheur. This instrument (fig. 1) has two parts:

Part 1, which resembles a cylinder bisected vertically, is called the semicylinder or female part. At the upper end are two screws, and handles in the form of two rings through which the assistant's fingers can hold the instrument steadily in place. It measures 11·0 cm. long.

Part 2 is a piston, which is 11·5 cm. long, and made in three different diameters—4·5, 5·0, or 6·0 mm. This is the male part.

The colporrhapheur helps to invaginate the medial part of the fascia, thus permitting the uninhibited use of the full thickness of the lateral parts of the fascia. When this is done in double layers, the bladder and urethra can be replaced in an upward and posterior direction, with lengthening of the urethra and formation of a new urethrovesical angle.

Operative Procedure

Through a midline incision the vaginal mucosa is carefully dissected up to the pubic rami, leaving the full thickness of the pubocervical, pubococcygeus, and puborectalis fascia attached to the urethra and bladder, which is usually thinned centrally. Hæmostasis must be meticulous.

The female part of the colporrhapheur is then introduced into the urethra and bladder up to 7 cm., the remaining 4 cm. being taken up by the handle. The male part is placed outside the urethra, in the midline and over the concavity of the female part, and held in place by applying the screws at the upper end of the handle.

The assistant, holding the handles of the colporrhapheur, now pushes its tip upwards with the pubis acting as fulcrum, thus lifting the urethra and base of the bladder, and invaginating them to expose the full thickness of the pubocervical fascia, Two rows of interrupted catgut sutures are placed deeply through the fascia,

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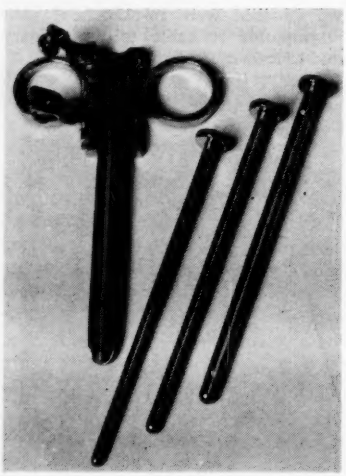

Fig. 1.

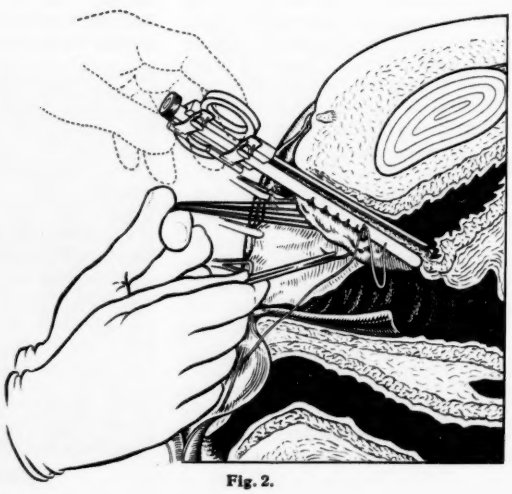

Fig. 2.

which bulges on either side of the colporrhapheur (fig. 2); after it is removed these stitches are tied and the vaginal mucosa is stitched. An indwelling catheter is used for 5 days.

Since 1958 I have used the colporrhapheur to operate on forty-eight cases with stress incontinence (and other associated pathological conditions), and so far this symptom has not recurred in any of them. Three patients had hæmatomas, and one had a pelvic abscess requiring drainage; apart from these complications superficial sloughing was seen in a few cases, but all these healed spontaneously. Retention of urine was usual for about 12 days after operation.

I should like to thank A. L. Hawkins & Co., Ltd., of 15, New Cavendish Street, London, W.1, for their cooperation in producing this instrument for me.

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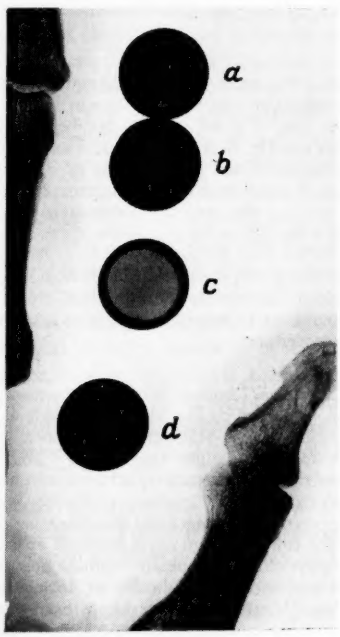
NEW STANDARDS FOR ESTIMATING BONE DENSITY

VARIOUS materials have been advocated for estimating the mineral content of bone from its X-ray shadow. Acting on a suggestion of E. A. Parke, Stein [1] employed an ivory wedge, tapering from 3 to 30 mm. in steps of 2 mm. For adult pelves, femurs, and spines additional ivory layers were taken. Ivory and living bone were placed side by side and a radiograph was taken on which densities could be compared. Mack [2] found that the transmission of ivory did not resemble that of bone as closely as was assumed originally, and replaced ivory by aluminium. Reich et al.[3] suggested replacement of the aluminium wedge by one of calcium chloride for the same reason. Post uses a vacuum-dried finger wrapped in opaque 'Cellophane'.[4]



Use of bone-density standards.
a contains 0·66 g.; *b*, 1·10 g.; *c*, 0·52 g.; and *d*, 0·79 g. of apatite per. sq. cm.

The new standards [5] are bone contained in open-ended tubes of stainless steel, which is opaque to X rays. The mineral content of the bone is reckoned as grammes apatite per square centimetre of the shadow cast. The standards are photographed together with the living bone, the steel tubes indicating the correct positions of the standards. The apatite content of the living bone is estimated by comparing it with the densities of the standards, whose apatite content is known (see figure).

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Reviews of Books

Cholera

Its Pathology and Pathogenesis. S. N. DE, M.B., D.T.M., PH.D., professor of pathology, Medical College, Calcutta. Edinburgh: Oliver & Boyd. 1961. Pp. 141. 25*s*.

EVERY year Professor De sees more patients with cholera than most of us are likely to see in a lifetime, and this book is evidence that he has not wasted his opportunities. In his introduction he points out that it was not some heaven-sent epidemiological inspiration which caused John Snow to remove the handle of the Broad Street pump but sound reasoning based on his own pathological observations. In the same spirit Professor De's argument is founded on his own work in the postmortem room and on the elegant experiments which he describes in detail. His major discovery is that the diarrhœa of cholera is due to an enterotoxin (which has many of the characters of an exotoxin) while the circulatory collapse and other features may be ascribed to an endotoxin. His methods and his reasoning are in the best traditions of classical pathology.

Saline infusion (popularised by Rogers but dating at least from Snow's time) is still the sheet anchor of treatment. To this Professor De would add antibiotics and cortical hormone but he admits that in spite of the relative abundance of his material he has not yet enough for a controlled trial. He adds many interesting observations on choleraic nephritis, but this remains to him (as to everyone else) an unsolved mystery.

If the global epidemiology of cholera receives least attention in this book it is because Professor De does not dogmatise about things of which he has no personal experience. (Those who are interested should consult Dr. Pollitzer's review.[1]) The problems local to Calcutta he knows very well and illustrates with some revealing photographs. There cholera is a disease of the hot weather before the monsoon breaks, but it is never absent nor is likely to be until both water-supply and drainage are improved. Professor De dislikes the name "asiatic cholera" because outbreaks affect other continents which seem to have no connection with an asiatic source (e.g., the last epidemic in Egypt). In Bengal the convalescent or ambulatory patient is probably responsible for the persistence of the disease but such patients are seldom if ever infectious for more than a few weeks: the factor which converts endemic to epidemic disease is still unknown. Nevertheless the historical evidence that the ripples which lapped the shores of Great Britain in 1831, 1854, and 1866 arose from a stone dropped in the Hooghli is strong.

This book is easy to read, nicely produced, and contains a delightful portrait of John Snow.

Surgical Gastroenterology

WARNER F. BOWERS, M.D., M.SC., PH.D., chief, general surgical service, Tripler U.S. Army Hospital, Honolulu. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 498. 148*s*.

ONE of Dr. Bowers' experiences will be familiar to many surgeons—the decision for or against surgery in a patient with gastrointestinal disease is often made before a surgeon is asked to see the patient. He has written this book, therefore, to give physicians and general practitioners a clearer insight into what surgery can achieve in gastrointestinal disorder, so that, failing early consultation, those who disdain surgical opinion will at least be better informed about indications and occasions. And if they read this book they will know of one informed surgeon worth meeting for his knowledge and opinion alone. Some might find Dr. Bowers' opinions too sharp on certain points—the dismissal of such terms as empyema of the gall-bladder, for example—but his attitude is not unreasonable and has the merit of directness.

The book is planned mainly on anatomical lines, so that each viscus is considered consecutively from above downwards

1. *Wld Hlth Org. Monogr. Ser.* 1959, no. 43; see *Lancet*, 1959, ii, 953.

after an initial section labelled " fundamental aspects ", but containing also the " odds and bobs " for which no place may be found in the anatomical sequence—such as parasites, trauma, foreign bodies, and ileal substitutes for the bladder. Oddly there is a final chapter on herniæ, included only because of their possible intestinal contents, otherwise an irrelevancy.

Too detailed for most general practitioners, the book is really one for specialists and postgraduate students, and possibly for the undergraduate looking for detailed information to enlighten a case. It is readable; and the only fault lies in the bibliography which seems to neglect work outside the author's own country.

Man's Presumptuous Brain

An Evolutionary Interpretation of Psychosomatic Disease. A. T. W. SIMEONS, M.D. London: Longmans, Green. 1960. Pp. 281. 25*s*.

THE group of diseases nowadays termed psychosomatic comprise, according to the author's definition, those found in modern civilised man and not normally appearing in wild animals in the free state. As they account for a great deal, if not the bulk, of the town-dweller's ill-health and mortality, the theory developed in this book that man's remote ancestors got us all into this contemporary psychosomatic fix some half a million years back is a challenging one. The fatal step in evolution was the over-specialisation of the human brain cortex, with which the more primitive diencephalon could not keep pace. Dr. Simeons sees the subsequent story of mankind as the battle between the Cortex and the Diencephalon, both of which are almost personified in his pages. Like Milton's Satan, the cortex is no end of a devil but never a bore. The diencephalon does its best to keep our bodies working smoothly and in the account of the evolution of various psychosomatic disorders we can observe how the cortex invariably throws a spanner in the works.

The opening account of man's bodily and mental evolution is well written and interesting, and though some of the subsequent chapters contain debatable views on the origin of disease, there is much sound sense also. The book should appeal to lay people and doctors alike.

Primitive Physic or An Easy and Natural Method of Curing Most Diseases

JOHN WESLEY. With an introduction by A. WESLEY HILL, M.B. London: Epworth Press. 1960. Pp. 125. 12*s*. 6*d*.

IT may seem a little strange that one of the most successful books on domestic medicine that has ever been written should come from the pen, not of a doctor, but of a preacher. In 1747, however, when *Primitive Physick* was first published, the distinction between a professional physician and an amateur was less distinct than it is today. Any well-educated gentleman might claim to be as familiar with the basic principles of physic as his practitioner: and if, in a given case, the assistance of the doctor was invoked, the intervention was more often reflected in the cost of the illness than in its prognosis. For fees were high, and many of the medicines prescribed were very costly. (Theriaca, to mention only one remedy which was much esteemed, contained over sixty ingredients. Its manufacture would have been an expensive business even if all of them had been easily available—and they were not.)

Wesley's aim, in writing his treatise, was to make available to his followers " an Easy and Natural Way of Curing Most Diseases " based either on his own experience, or upon the leading professional opinions of the time. It is evident to this day that many of his remedies had a certain efficacy. And when the advice given seems ridiculous, the famous divine is not always to blame. In advocating for the " iliac passion ", that a live puppy should be held to the belly, he was only quoting Sydenham.

It is perhaps too much to hope that the new volume will repeat the success of the original work. That ran to twenty-three editions in the author's lifetime and to nine more subsequently. But Dr. Wesley Hill is to be commended for having made generally available once more a notable commentary on the status of medicine in the eighteenth century.

Office Diagnosis

PAUL WILLIAMSON, M.D. Philadelphia and London: W. B. Saunders. 1960. Pp. 470. 87*s*. 6*d*.

A GENERAL practitioner in the United States, Dr. Williamson, has written a series of short essays on the diagnosis of conditions commonly seen in his surgery. The book is not intended to be comprehensive but it covers a wide range, from dysmenorrhœa and angina pectoris to obesity and pneumothorax. In part the selection has depended on the frequency of the conditions, and in part on the author's interest in them. After reading this book, one is left in no doubt that Dr. Williamson is a " good " doctor. His scientific knowledge is on the whole sound and his knowledge of human beings even sounder: he sees his patients as a whole; he is well balanced, with few bees in his bonnet, and his enthusiasm is refreshing and tempered with wisdom. He writes in a pleasant free-and-easy style. Many practitioners in this country and final-year students could read this book with interest and intellectual profit, though they may be alarmed by the price. Dr. Williamson is to be congratulated and envied, for only a happy man who loves his work can write as well as this.

Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment (5th ed. Edinburgh: E. & S. Livingstone. 1960. Pp. 288. 37*s*. 6*d*.).—This excellent little book by Dr. H. J. Parish and Dr. S. A. Cannon gives a full but short and balanced account of the main means of specific therapy and prophylaxis of infective disease by immunological methods. Dr. Parish says that this subject is often considered hard to master: this book should go far to dispose of the difficulties. It is particularly valuable for casualty doctors, general practitioners, and those working in public health. Although the principles of immunology are clearly brought out, this is essentially a practical handbook to help the man who is actually going to carry out the procedures.

Children for the Childless (London: William Heinemann. 1960. Pp. 210. 12*s*. 6*d*.).—Edited by Dr. Morris Fishbein and revised for this country by Mr. J. Stallworthy, this book, to which nine authorities contribute eight chapters, is " anglicised " in scarcely more than words and, is, in essentials, not only by but for citizens of the U.S.A. It takes a very wide view of its subject. A chapter on the advantages and disadvantages of having children, and how to bring them up, is followed by one on the anatomy and physiology of human reproduction in which the average measurements in minutes or inches of everything is set down. Fertility and sterility, the world population problem, artificial insemination, adoption, inheritance, especially of Mendelian characters, are all set forth; and emotional aspects of the various subjects are not neglected. The book is, in fact, full of information on almost everything connected with or arising from human reproduction, but it is for those who want to know rather than for those needing help, and it will perhaps not greatly assist an " ordinary " married couple in this country, childless and desiring a child.

Mental Health Act, 1959 (London: The Institute of Hospital Administrators, 75, Portland Place, London, W.1. 1960. Pp. 138. 13*s*. 6*d*., post free 14*s*.).—Mr. S. R. Speller has republished the series of articles describing this important but complex new Act which he contributed to *The Hospital* during the past two years. The book is a useful summary of the whole Act; but, as it was written with members and officers of hospital and local health authorities especially in mind, the sections which deal with their interests are the most detailed. Relevant parts of the Act and some regulations are quoted verbatim. There is a helpful index.

THE LANCET

LONDON 18 FEBRUARY 1961

Impartial Information

"Should anything be done about the pressure on doctors by modern methods of salesmanship brought to bear by the drug houses? Is sufficient information and advice available to doctors to enable them to put the claims of drug manufacturers into their proper perspective and, if not, who should provide it?"

THESE questions, asked and partly answered by the Hinchliffe Committee,[1] remain very important because we cannot reasonably rely on the manufacturers both to produce new drugs and to describe them in an entirely disinterested way. Now large and powerful, the pharmaceutical industry comprises firms with a high sense of duty but also some with a high sense of profit. It spends a great deal of money, takes big risks, and occasionally produces results of outstanding value. Besides benefiting patients, these successes have sometimes led to vast economies in medical care; and, in the hope that they will continue, most of us are willing to accept the disadvantages inseparable from a competitive industry. At the same time we are resolved that medical practice shall preserve a proper independence of business. The pharmaceutical industry, conscious of what its contributions can mean, may be pardoned if it sometimes comes to think of the practitioner as an agent or distributor, whose most useful function nowadays is to apply its latest discovery. Compared with devising and producing a new drug, persuasion of the doctor may even seem a relatively small matter, for which the techniques of ordinary advertising will suffice. To the profession, however, a fresh remedy is only an addition to the great number of existing means of aiding patients; and the duty of the professional man is to use his judgment on each innovation, with some of the scepticism in which he has been trained. We are probably the gainers from a system in which manufacturers have a certain eagerness in the sale of their products; but, to balance this, we must have means whereby their claims get critical scrutiny. To return to the Hinchliffe Committee's questions, are we satisfied that we have?

Everybody agreed with the committee that "new drugs should be subjected to independent controlled clinical trial as early as possible"; and most of us agreed also with their suggestion that professional bodies should take the responsibility of advising doctors on the value of the drugs. Where arrangements for clinical trials are made by the manufacturers themselves, it seems particularly desirable that there should be an external interpretation of the results. One way of introducing a new product, which seems to be gaining currency, is for the firm concerned to hold a conference—perhaps at one of the centres where the drug has been studied—at which papers are read by the people (including doctors) who have made the various forms of test; but, though this kind of conference concentrates a variety of experience, and the names of participating authorities often carry weight, it still does not really offer any external interpretation; for the circumstances are such that a new remedy is almost bound to be given the benefit of any doubt. This is particularly likely, also, in trials where the investigator receives a fee or where a grant towards costs is considerably to his advantage. The Hinchliffe Committee did not define the rather tenuous boundary between fees and expenses, but it stated clearly and correctly that doctors should not be paid by the manufacturers for participating in clinical trials. This has a bearing also on the terms on which pharmaceutical firms may be encouraged to support the pharmacological departments of medical schools. These departments often need money, and some manufacturers have managed to give it to them without any strings at all: but we know of at least one university department (not in this country) where critical work seems to have been inhibited by the way in which the department is financed; and we should ourselves regard any such departure from academic freedom as disastrous. In the long run the medical schools, with their inculcation of the scientific attitude, are the chief safeguard of our sense of proportion—often too easily disturbed.

Assuming that clinical trials are made in one of the ways the Hinchliffe Committee thought satisfactory, how can the doctor be given the results so that he will always be properly informed before he uses a new drug? Some manufacturers will give him the facts with remarkable objectivity in their leaflets, but others will be inclined to look on the bright side. Others again are more concerned with their trading returns than with the improvement of practice. As an alternative, doctors have their medical journals; but in using these they should understand that acceptance of an advertisement by such a journal does not imply that the editor advises that the drug should now be used: it means only that he thinks that a case has been made out for presenting the product to his readers—a critical audience able to judge for themselves. The practice of different journals differs, and in this difficult matter of symbiosis with advertisers most of them will admit to being sometimes too tolerant, though advertisers may complain of their being too authoritarian. Readers may be right in regarding too much licence as more harmful than too much censorship; but an editor who believes in reasonable freedom of speech for his advertisers can at any rate practise the same freedom in his editorial columns. Here any advice given, whether good or bad, is likely to be wholly detached; and the same is true of the regular comments on pharmaceutical innovations which some of our contemporaries usefully provide. In one way and another readers of the general medical journals eventually get a lot of well-informed comment on new preparations; but the Hinchliffe Committee was

1. Ministry of Health: Final Report of the Committee on Cost of Prescribing. H.M. Stationery Office, 1959.

nevertheless correct in speaking of the dearth of impartial information in a convenient and readily accessible form.

For some years we have had *Prescribers' Notes* from the Ministry of Health, and within their rather official limits these have been very useful. But the need is clearly for much more comprehensive news of trials, with independent guidance based neither on a wish to sell a drug nor on a wish to reduce expenditure. Hence the committee did well to recommend that the *Notes* should be replaced by an independent professional journal which would be produced by a small council—perhaps appointed by the appropriate professional bodies—with a whole-time editor. Though this journal was to be run " by the medical profession for the profession ", the committee thought it should be published, distributed, and partly paid for by the Ministry of Health. We hope that the result of present plans may prove that such arrangements are compatible with its being unofficially authoritative, and (when necessary) passionately dispassionate. We understand that the publication will be named the *Prescribers' Journal* and will be published two-monthly.

Meanwhile probably the nearest approach to what is wanted is the *Medical Letter*, published fortnightly from New York by Drug and Therapeutic Information, a non-profit corporation.[2] Somewhat resembling typescript in appearance, this has the psychological merit of looking like one of those news-sheets sent to subscribers who are prepared to pay for inside information on the world's events. Its four pages can be read quite quickly before they are filed for reference, but they have been written with the kind of care essential in offering such advice:

" As one of the first steps in the evaluation of a drug, the medical director of the company that makes it is asked for any data on the drug he cares to submit. When a preliminary draft of the appraisal is sent for review to the members of the *Medical Letter* Editorial and Advisory Boards and to special consultants, a copy is sent at the same time to the medical director of the company for his comments. Most of the companies promptly supply information about their products; and in their comments on the drafts, the medical directors frequently make useful criticisms and suggestions. Probably the sharpest disagreement has been over the adequacy of controls in clinical trials."

Though published in the United States, the *Medical Letter* contains much information equally useful in this country. Hence we view with strong approval the action of the Northern Ireland General Health Services Board in circulating copies to all the doctors on its list. Since last April the fortnightly issues, received in Belfast within a few days of publication, have been immediately reproduced, on rather smaller pages, for practitioners in Northern Ireland. We shall be surprised if, in making this wise contribution to better practice, the board has not at the same time promoted proper economy.

2. The managing director is Mr. Arthur Kallet, and the editorial board Prof. N. M. Greene, Dr. P. H. Lavietes, and Dr. Harold Aaron. The address is 136, East 57th Street, New York 22, N.Y., U.S.A. Subscriptions: $12.50 for one year; half-price for residents, interns, and students.

Unmarried Mothers—and their Children

THE less people know about illegitimacy the more they tend to have strong feelings about it: this is the conclusion of VIRGINIA WIMPERIS, who has just written a comprehensive book [1] on the subject. The facts she presents should accordingly be made widely known. In England and Wales there are now more illegitimate births than there were before the war. As in many other countries, including Switzerland, Scandinavia, Western Germany, the United States, Australia, New Zealand, South Africa, and Canada, both the number of illegitimate births and their proportion of all births are rising. In England and Wales 1 child in 20 is born illegitimate: 1 in 8 is conceived outside marriage. 1 mother in 4 conceives her firstborn child before she is married. Among the children below school-leaving age, over 500,000 are illegitimate.

These figures, though suggestive, cannot be taken at their face value either as an accurate account of illegitimate births or as a measure of illegitimacy as a social problem. For one thing, they are probably an underestimate. Women have babies by men other than their husbands. A woman can adopt her lover's surname and register her child jointly with him as though they were married; the registrar does not ask to see the marriage lines, and if he asks for the date of marriage he may be given a fictitious one. And some mothers manage to conceal the birth of their babies. These figures also include many children who are illegitimate for only a few days or months. They include the child who grows up in a stable home with both parents, and also the child of an unknown father who grows up separated from his mother.

A rising illegitimacy-rate is sometimes cited as an index of increasing immorality. But there is very little evidence that this is so.[1] For instance, the illegitimacy-rate in England and Wales rose from 4·2% in 1938 to 9·3% in 1945. But there was no increase in the number of unmarried women who became pregnant and no increase (in fact, a slight decrease) in the number of children born of irregular conceptions. What happened was that fewer couples who had conceived a child were able to marry before its birth. Many of these extra illegitimate pregnancies were later regularised by marriage.

Illegitimacy does not show a constant correlation with poverty, climate, or religion. The rates in the East End of London have been consistently lower than in the West End. Rich Sweden's rate is consistently about three times that of poor Italy. It is not commoner in " hot-blooded " countries. The rates are approximately the same in Scotland and Spain, and are seventeen times higher in Iceland than in Greece. Some Roman Catholic countries, including Eire, Italy, and Belgium, have low rates; but in Portugal the rate is 15·6% and in Austria 20·9%. The same is true of Protestant countries. The rate in Iceland is 23·7%, in Holland, 1·5%. Low mentality also seems to play a small part in illegitimacy.

1. The Unmarried Mother and Her Child. By VIRGINIA WIMPERIS. London: Allen & Unwin. 1960. Pp. 397. 35*s*.

The two tend to be associated in people's minds because when they do coincide the combination often causes trouble. Although some 4000 illegitimate children of mental defectives are believed to be in the care of local authorities, yet only about 0·5% of all the mothers of illegitimate children are unmarried ascertained defective women. This is rather less than the estimated proportion of mental defectives in the population as a whole.

The underlying causes of illegitimacy seem to differ widely from time to time and from place to place, and many factors contribute, including the relative numbers of men and women of marriageable age, local customs, and the flux of population; and it is therefore hard to generalise. Detailed sociological studies in each area are needed to provide their own explanations.

BOWLBY [2] divides illegitimacy in Western communities into two types—one socially acceptable and the other socially inacceptable, the former including children born in communities with the convention that before a girl marries she should demonstrate her fertility. From the practical viewpoint, one big problem is how to reduce the incidence of illegitimate births, particularly the "socially inacceptable" kind that are likely to handicap the children concerned. All of the many ways in which the illegitimacy-rate could be lowered would raise other difficulties. In the past, public opinion has been the chief force. In the West Indies and in parts of South America more than 60% of all births are illegitimate and public opinion accepts it. But if public opinion is strongly against illegitimate births it is liable, as in the past, to create a mental climate in which there is little chance for illegitimate children to grow up healthy and happy. Forced marriages also reduce the incidence of illegitimacy—but tend to produce unhappy marriages, divorce, and separations, and thus eventually new illegitimate children. Early marriage is another preventive, but this is known to lead to more divorce, and also probably to faithlessness. Legalised abortion, another theoretical if partial solution, would bring many added complications. So would easier divorce, which WIMPERIS believes would do more than any other single reform to reduce the illegitimacy-rate "by a stroke of the pen, to under 3% of all live births".

WIMPERIS suggests that ultimately stable, loving homes are the best prophylactic. Meanwhile the most controversial related issue is that of birth-control. There is the difficult question of how far it is desirable to instruct adolescents and the unmarried in its use. And opinion is sharply divided about the effect that wider knowledge and practice of birth-control would have on the illegitimate-birth rate. CREW [3] emphasised that the illegitimacy-rate is an index of the ignorance that prevails concerning contraception and that this is society's direct responsibility. In Sweden the deliberate spread of knowledge of sex and birth-control brought about a sharp fall in illegitimacy, despite coincidental far-reaching measures to make life economically easier for unmarried mothers and their children.[4] There is some evidence that the same would happen here. After 1870, when the growth in the practice of birth-control first began to reduce the birth-rate, there was a sharp decline in the proportion of unmarried women who became pregnant. On the other hand, our illegitimate-birth rate is much lower than Sweden's and we probably have a higher proportion of unmarried mothers who are mentally subnormal or who have neurotic or compulsive pregnancies,[1] and who would be unlikely to practice birth-control effectively.

The other big practical matter is how best to give the illegitimate child the best possible chance in life. Here the situation has changed tremendously during the past century. The longstanding tendency to punish the child, both legally and socially, for the conduct of the parents is vanishing. Generally speaking, there is practically no activity to which illegitimacy, per se, constitutes an absolute barrier.[5] Since its foundation in 1918, the National Council for the Unmarried Mother and her Child [6] has campaigned ceaselessly and successfully, and has also helped thousands of unmarried mothers and their children.[7] Nevertheless, the fatherless child and his unmarried mother are still seriously handicapped in our society. WIMPERIS doubts whether these mothers as a group are as neurotic as YOUNG [8] and BOWLBY [2] have suggested, and she points to the grave economic problems in the situation, and the way they are dealt with at present. Many unmarried mothers are helped by their families, and some by friends. But if this is not possible, the child who remains with his mother is unlikely to be brought up in a stable environment. It is very hard for a single woman with a child to find a suitable job; and it is even more difficult for her to find accommodation. She probably does best if she is suited by training and temperament to domestic work and is lucky enough to find a post where she can make a home for her child; but such arrangements are rarely feasible. Meanwhile, the practice of providing State-subsidised day-nursery accommodation for the child, to enable the mother to be separated from it during the day, is of doubtful value to both, and also to the State. Such accommodation now costs approximately 21*s.* per child per day,[9] more than the mother is likely to earn. BOWLBY has suggested that day care as a means of helping the husbandless mother should be restricted to children over three. Until the child has reached this age, direct economic assistance should be given to the mother.[2] But to many this might be regarded as the direct subsidising of irresponsible parents, and, despite the evidence to the contrary, as an encouragement of sin.

2. Bowlby, J. Maternal Care and Mental Health. World Health Organisation, 1951.
3. Crew, F. A. E. Measurements of the Public Health. Edinburgh, 1948.
4. Myrdal, A. Nation and Family: The Swedish Experiment in Democratic Family Policy. London, 1945.
5. Jeger, L. M. Illegitimate Children and Their Parents. National Council for the Unmarried Mother and Her Child, 1951.
6. The Council's new address is 455, Kentish Town Road, London, N.W.5. (GULLiver 8166).
7. Fisher, L. Twenty-one Years and After, 1918–1946: the Story of the National Council for the Unmarried Mother and Her Child. 1946.
8. Young, L. *in* Understanding the Psychology of the Unmarried Mother. Family Service Association. New York, 1947.
9. Selwyn-Clarke, Lady. *in* Working Wives: what of the children? National Society of Children's Nurseries, 1960.

Annotations

COLLEGE OR DIVISION?

THE question whether pathologists are to found a college of their own affects many besides themselves. The arguments on both sides were set out in our columns fairly fully last October and November, before the referendum held by the Association of Clinical Pathologists.

In this referendum, from an electorate of 1162, the number voting was 838, but this gave no clear majority. Of the voters, just under half (415) favoured the establishment of an independent college, while 350 favoured the creation of a faculty within the Royal College of Physicians; but, including the votes of those willing to accept a majority decision and of those with no strong preference, 681 were prepared to support a faculty, compared with 669 prepared to support an independent college. The council of the Association appointed a working party to promote the formation of an independent college of pathology; but Dr. E. N. Allott, their chairman, regarded the majority as insufficient for such action. In a letter resigning his chairmanship he pointed out that "rather over one-third of the membership favoured an independent college, while slightly less than one-third favoured a faculty within the Royal College of Physicians, and one-third expressed no opinion or abstained from voting".

Hitherto no corporate opinion has been expressed by the Pathological Society, and we learn with interest that this is now to put the same questions to its members in a similar referendum. Believing as we do that the function of colleges is to integrate the profession rather than fragment it,[1] we are glad to know that the Royal College of Physicians remains ready to consider whatever pathologists may reasonably ask of it.

RUPTURE OF THE KIDNEY

"ANY trend towards safe and wise conservatism in the management of the results of trauma must inevitably evoke approval and satisfaction." This quotation of the late Sir Gordon Gordon-Taylor forms an apt preface to a review by Opit et al.[2] of 77 cases of closed renal injury treated at the Royal Adelaide Hospital in which surgical interference was withheld as far as possible, with good results. Most British urologists will agree with this policy; but others recommend early exploration, not only as a potential life-saving measure, but also to avoid the hypothetical risk of chronic renal damage and subsequent hypertension. General experience indicates that the number of ruptured kidneys requiring immediate surgery is probably small, except where the renal injury is associated with multiple internal injuries. In this respect Opit et al. may have been fortunate, since urgent operation for suspected intraperitoneal bleeding was necessary in only 2 cases, and in 1 of these the injured kidney was conserved. 3 other patients were subjected to delayed exploration on account of persistent hæmaturia and in 1 of these the damaged kidney was removed. No patient died.

As regards the danger of late complications, and particularly the risk of hypertension, the position is rather less clear. Few long-term follow-ups of patients who have recovered from renal trauma have been recorded, and in these it is often difficult to collate any subsequent complications with the extent of the original damage. In the present series 34 of the 77 patients were reviewed after a year or longer, and hypertension was found to have developed in only 1. All the others remained free from renal complications, though in 5 pyelography continued to show gross abnormalities.

In their plea for conservatism Opit et al. tend to decry routine pyelography, especially by the retrograde route, as a means of early assessment. They rightly point out that instrumental procedures may be responsible for many of the complications cited by those who advocate early surgery, and they suggest that excretion pyelography may be contraindicated or prove uninformative in severely shocked patients with serious hæmorrhage. In their opinion radiographic studies are best conducted during the period of recovery, with a view to determining the need for delayed interference or establishing a record for future reference.

CARE OF THE INJURED

THE accident services of this country have lately been scrutinised by several authorities. The committee appointed by the British Orthopædic Association[1] thought they would be improved by the designation of a relatively few hospitals for the treatment of serious casualties. Its report discountenanced the present role of a multitude of smaller institutions, and made no suggestion about the inclusion, in any future service, of the voluntary first-aid organisations throughout the British Isles.

In the first Ruscoe Clarke lecture[2] Sir Alexander Drummond, Director-General of Army Medical Services, criticises these findings and points to the vast experience in the care of the injured which the Army Medical Services have acquired. It would be folly, he said, to ignore this. Faced with the necessity of dealing not only with civil incidents but also with the effects of modern conventional and nuclear weapons, the Forces have, since 1955, been training their personnel in appropriate first-aid methods. Even so, the Cyprus operations showed that there were five common faults in the early treatment of casualties: (1) failure to secure an adequate airway; (2) poor positioning of unconscious patients, who were liable to inhale their secretions; (3) ineffective immobilisation of fractures and soft-tissue injuries; (4) over-sedation; and (5) a tendency to give fluids by mouth when it was inadvisable to do so.

To raise first-aid standards, R.A.M.C. recruits now devote more time to this subject. Tuition centres on a more realistic simulation of injuries in mock casualties, and a standardised technique for such procedures as gastric suction or the administration of intravenous fluids. The early and adequate replacement of blood has also been studied. During the Suez fighting the time which elapsed after a man was wounded until he had been evacuated by naval helicopter and placed in a hospital berth with a drip set up was sometimes as little as fifteen minutes. In the Cyprus operations of 1956 the period between wounding and transfusion in a military hospital averaged one hour. Supplies of blood might be limited in war or in a major disaster, but work at the United

1. *Lancet*, 1951, ii, 1071.
2. Opit, L. J., McKenna, K. P., Nairn, D. E. *Brit. J. Surg.* 1960, **48**, 240.

1. *J. Bone Jt Surg.* 1959, **41B**, 458; see *Lancet*, 1959, ii, 75, 78.
2. *J. R. Army med. Cps*, 1961, **107**, 35.

States Naval Hospital at Chelsea, Massachusetts, has shown that stockpiling, against the hour of need, is quite feasible. Cells can be separated from plasma, mixed with glycerin, and frozen. Cells and plasma can then be stored separately for several years, and will still yield an acceptable substitute for fresh blood when reconstituted. The R.A.M.C. are investigating, at Millbank, a method for storing blood in liquid nitrogen.

Public and medical opinion, Sir Alexander felt, would not allow small hospitals to be completely by-passed in any scheme which might be introduced. But there might be hospitals where, since the standard of accident care was low, other departments were likely to be less than first-class. Such institutions might with advantage be "taken over" by larger hospitals, which would assume responsibility for their equipment, sterile supplies, and maintenance. This system of supply has been working very successfully in Army hospitals.

To secure a concerted effort, the principle of control or guidance over the management of the injured had to be accepted. Such control of an accident service should be vested in an eminent consultant, who should ideally be a general surgeon. He would weld those about him into a team, and his would be the responsibility, not of directing what treatment patients received, but of ensuring that policy, training, research, and emergency cover were suitably coordinated in a number of establishments which might be scattered over many square miles.

EMERGENCY AIRWAY

SUDDEN complete respiratory obstruction will cause death or irreversible damage unless it is relieved within about four minutes. This leaves no time for fumbling or for summoning medical aid: the man on the spot must act at once. The action which he should take has been studied in the Medical Service School of the United States Army. The recommended procedure [1] comprises four steps. The first step consists in establishing that critical airway obstruction exists; and its presence is inferred from such signs as cyanosis, stridor, absence of airflow, straining of chest and neck muscles, and unconsciousness. The second step consists in attempts to relieve the obstruction by digital removal of foreign matter and positioning of the head and neck. The third step is the application of positive-pressure artificial respiration, by the mouth-to-mouth or mask-and-bag method; persisting partial obstruction may be relieved by adequate inflation pressures. The final step, to be taken if the victim's life is still in danger, is puncture of the cricothyroid membrane. This method of bypassing upper-respiratory obstruction has several advantages, in the circumstances envisaged, over tracheotomy. The position of the membrane is said to be easily identified by the layman between the prominences of the thyroid and cricoid cartilages. It can be punctured with scissors, a pocket-knife, or even a nail file, and no important blood-vessels or nerves are in its immediate vicinity.

The American authorities have gone much further than ours in their plans to teach life-saving measures to non-medical personnel. They have found—not surprisingly—that few laymen can learn to do an emergency tracheotomy. Apparently, however, the simpler procedure of cricothyroid puncture can be taught to laymen.

1. Nicholas, T. H., Rumer, G. F. *J. Amer. med. Ass.* 1960, **174**, 1930.

BLOOD-PRESSURE AND ENVIRONMENT

RECENT controversies on the role of heredity in essential hypertension have underlined the many sources of error both in the measurement of blood-pressure and in the statistical analysis of the readings obtained. But they have not provided any positive information about the nature of the hypertension, and since it is still easier to change one's environment than one's ancestors it may be desirable to pay a little more heed to the former. Here again the problem is not straightforward; for an individual's blood-pressure is not fixed but varies incessantly about a mean which may, but often does not, coincide with the casual reading.

The stress of civilisation is widely believed to be bad for the blood-pressure; and the case of the American Negro, who is prone to hypertension and its complications, is often cited as supporting this belief. But "stress" and "civilisation" are portmanteau words which have no scientific meaning until they are, so to speak, unpacked and their contents are itemised.

With such considerations in mind Dr. Lowenstein (whose article appears in this issue on p. 389) has carefully studied the effects of age and sex on the blood-pressures of two Brazilian tribes—one relatively civilised by missionary influence, the other pagan and uncultured—and has also summarised twenty-five other papers relating to inhabitants of tropical and subtropical climates. His own results show a rise of pressure with age, especially in males, only in the civilised group. The other studies mostly showed a similar tendency, but in four groups in which the pressure did not rise with age the subjects were small homogeneous populations living in primitive isolation. On the other hand, in recent studies of a rural community in Nigeria [1 2] the blood-pressure was found to be much the same as in a European community, rising with age; and hypertension was common, though coronary thrombosis was rare. Frank myocardial infarction has also been found to be rare in the South African Bantu,[3] though diffuse myocardial fibrosis with heart-failure was relatively common. Dr. Wainwright points out, however (in an article on p. 366) that this last is not necessarily a result of atheroma, which he finds less severe in the Bantu than in the European. On the other hand Dr. Bouchier and Dr. Bronte-Stewart (p. 363) find that coronary ischæmia is related not to race but to an individual tendency to alimentary lipæmia. But atheroma is a separate problem, and its association with hypertension is probably due not to a common ætiology but to the fact that the location and severity of atheromatous deposits are chiefly determined by intravascular tension.

Much further field work must be undertaken before these problems can be clarified. Meanwhile, it is interesting to note that, although the Nigerians studied by Abrahams et al.[1 2] were illiterate and uncivilised, they partook freely of the rock salt which is plentiful in the district; whereas Dr. Lowenstein's primitive Carajas had to make do with plant ash (potassium chloride). Those who suspect that the life of a starving native surrounded by man-eating fauna is almost as stressful as that of a high-pressure business executive may wonder whether the baneful effect of "civilisation" on blood-pressure is not perhaps, after all, simply a matter of salt intake.

1. Abrahams, D. G., Alele, C. A., Barnard, B. G. *W. Afr. med. J.* 1960, **9**, 45.
2. Abrahams, D. G., Alele, C. A. *ibid.* p. 183.
3. Laurie, W., Woods, J. D., Roach, G. *Amer. J. Cardiol.* 1960, **5**, 4.

FOOD-POISONING

JUST as last year was the wettest for many years, so 1959 was the warmest; but the continued sunshine and high temperatures seem to have had little observable influence on the public health for good or ill. Of all diseases food-poisoning might be thought to be especially susceptible to climatic influences, and it is true that the recorded incidence in 1959 rose by 7% over that in the previous year. The incidence was, as always, greatest between July and September, and while these are our hottest months they are also the months when communal and alfresco feeding are most prevalent. We should have sounder ideas on the effects of climate (and of national custom and diet) on the incidence of food-poisoning if any other country published such an illuminating review as the annual report produced by the epidemiological laboratory of the Public Health Laboratory Service.[1]

Those who are inclined to belittle the importance of food-poisoning should be reminded that there were 27 fatal infections in England and Wales in 1959. For some years, in fact, there have been more deaths from this cause than from diphtheria and typhoid fever together. Given public interest and sound discipline, all outbreaks of toxic food-poisoning due to staphylococci and clostridia are avoidable; but it is a measure of the distance to be made up that food-poisoning due to these causes is not uncommon in hospitals where surgical sterility receives daily and conscientious attention. Of the origins of salmonella food-poisoning we know more than we did, but this is not yet enough to frame any plan which would seem likely to lower its incidence effectively. The report points out that while *Salmonella typhimurium* still causes far more food-poisoning than any other member of the genus, the proportion of exotic species implicated is rising steadily. This is no doubt a reflection of a wider variety of food in the shops and increased foreign trade. We know that some imported meat, eggs, coconut, bone-meal, and protein residues contain salmonella in frightening numbers. We know too that more business-like methods of rearing livestock at home may encourage salmonella infections in calves. We eat more eggs and poultry than we did, and this report calls attention to human infections by *S. pullorum:* not only is this probably the most widespread of all the genus but it presents some practical problems to the bacteriologist which may cause it to be overlooked. Regarded quantitatively the problem is baffling if all salmonellæ behave like *S. typhimurium*. Few of us ever eat a meal shared with no-one else, and yet there were 6885 single infections with this organism, compared with 961 epidemics involving groups or families. We know little about the dose needed to produce disease in man, and even less about possible differences in individual susceptibility. Possibly we all eat salmonellæ every day, and gastro-enteritis is the result of some upset in a usually peaceful symbiosis. (But if this is so it is not easy to explain the epidemics involving several hundred people simultaneously.) For our ignorance we can blame our lack of energy or imagination, but some of the blame lies with the apathy of our fellow-citizens: 27 deaths from arsenical food-poisoning would create universal consternation.

One more detail in this report is worth mention. Of 607 outbreaks involving more than one person the cause of 42 was not discovered. Admittedly the bacteriologist does not always receive satisfactory material, but sometimes he may himself be to blame. Selective media have their dangers as well as their virtues, and occasional food-poisoning due to bacteria other than salmonellæ, staphylococci, and clostridia is well authenticated. Not enough specimens are submitted to chemical examination. Probably some causes of diarrhœa and vomiting are as yet unrecognised. Drinking-water contaminated with human fæces will produce symptoms of food-poisoning in the apparent absence of any pathogenic bacteria (although boiling the water appears to make it safe). Perhaps a similar phenomenon accounts for some instances of food-poisoning.

1. *Mon. Bull. Minist. Hlth Lab. Serv.* 1960, **19**, 224.

IS INACTIVITY ALWAYS MASTERLY?

THE patient unconscious from a recent severe head injury presents a pretty problem. It is relatively easy to examine him clinically and elicit what signs there are. It can often be said with fair confidence whether he will live or die if managed conservatively with good nursing. Certain well-defined complications can often be recognised and with appropriate measures localised and treated. But there remains a large group of cases in which neither the diagnosis nor the prognosis is certain. The vast majority of these patients will have cerebral "contusion"; but some will have sizeable intracerebral or subdural clots of blood, in some fatal extradural hæmatoma will be developing, and some few will have significant cerebral swelling which really should be treated.

Kristiansen and Tandon [1] have analysed 265 severe cases out of 3000 head injuries. The results reveal the extent of the problem. 164 patients were classed as operable because of the intracranial condition, 36 had depressed fractures which were mainly treated conservatively, and 65 cases of severe brain contusion and laceration were finally classed as "inoperable" because surgical treatment could not favourably influence the progress. Diagnosis of complications followed familiar lines of observation of level of consciousness, pupillary size and reactions, paralysis, and reflexes. Complete areflexia with absent corneal responses was almost always followed by death. Bilateral extensor plantar responses with or without extensor spasms were ominous but not irreversible: so also were dilated fixed pupils. The important point about the remaining cases was the impossibility in many of them of determining by clinical examination whether an operable complication was developing, and if so where the lesion was. The most useful diagnostic aid was an angiogram on one side with contralateral carotid compression; if necessary, the other side could be injected subsequently. This showed extradural and subdural hæmatoma, and was the only method of diagnosing preoperatively the situation of an intracerebral hæmatoma—though even then some of these were missed. Bilateral ptosis with downward deviation of the eyes and extensor plantar responses were associated with subdural hæmatoma in the posterior fossa.

Unoperated and non-fatal cases of cerebral contusion were not included in the series, which is therefore unrepresentative to that degree. Nevertheless the lessons are clear enough. Angiography is essential to the diagnosis of severe brain injury. If no large clot is present the patient may still require tracheostomy and hypothermia, which Kristiansen and Tandon found of great value. When and whether dehydration should be applied more vigorously than by simply withholding fluids is still not

1. Kristiansen, K., Tandon, P. *J. Oslo City Hosps*, 1960, **10**, 107.

clear. Studies of electrolytes have a place in long-continued coma.

The treatment of the severe head injury is clearly becoming less the province of the inactive master than it has been hitherto.

HYPOTHERMIA AND X-IRRADIATION

In their response to cooling animals fall into three groups: they may be homœotherms, keeping a fairly constant body-temperature regardless of the environment; they may be poikilotherms, their body-temperature tending to follow that of the environment; or they may exhibit each type of response at different times. Thus, hibernating mammals may be regarded as poikilotherms during the winter, and homœotherms during the summer. The newborn offsprings of many homœotherms pass through a poikilothermic stage lasting a few days, during which they can withstand transitory profound hypothermia.

The practical importance of this classification is that when homœotherms are cooled to body-temperatures of below about 15°C, their spontaneous respiratory and cardiac movements cease and they cannot be revived simply by warming. On the other hand, poikilotherms may be cooled to temperatures around 0°C and be more or less restored to their former state by rewarming. In poikilotherms, at body-temperatures below about 15°C, circulation and respiration continue at much lower rates. For instance, the number of heart-beats per minute in the hibernating bat (*Nyctalus leisleri*) at 4·1°C is 16, compared with 420 in the active animal at 37·3°C.[1] Although the metabolism in hibernating mammals is at a low level their requirements are also low, and the compensatory physiological mechanisms are such that they are adequately oxygenated. In contrast, when homœotherms and their newborn are cooled to below 15°C, circulatory and respiratory movements cease completely, but as the animals still have some metabolic requirements they tend to become profoundly hypoxic.[2] The resistance of animals to cooling has been ably reviewed by Smith.[3] Studies on the effects of various agents on cold mammals have until quite lately been limited to hibernators and newborn animals below 15°C, and to homœotherms above 15°C. This was because it was technically impossible to resuscitate homœotherms which had been cooled to, and maintained at, temperatures much below 15°C. In 1949 Giaja and Andjus [4] described how rats cooled to 1°C in two stages could be reanimated by applying a hot spatula to the precordium and insufflating the lungs. Only about 25% of the rats were resuscitated by this technique, and few of these survived longer than several days. Later, Andjus and Lovelock [5] and Goldsveig and Smith[6] developed less traumatic methods for resuscitating small, ice-cold mammals, some 80% of which survived.

Much radiobiological work has shown that the sensitivity of cells and tissues to X-irradiation is considerably modified by the amount of oxygen in them.[7] Well-oxygenated tissues are approximately three times as sensitive to ionising radiations as anoxic tissues. The modifying effects of cold on X-irradiated animals has been reviewed by Weiss.[8] Doull and Dubois [9] studied the effects of X-irradiation on hibernating ground squirrels (*Citellus tridecemlineatus*). This work, in common with other studies on hibernating mammals, showed that the appearance of irradiation damage is greatly delayed, but that it appears in full when the animals are warmed to be the "active state" and no ultimate protection is afforded by hibernation. Osborn and Kimeldorf [10] found that hibernation induced after exposure to radiation also delayed the onset of damage, but again provided no ultimate protection. In terms of tissue oxygenation, these findings were to be expected. In 1941 Evans et al.[11] demonstrated a distinct increase in the radioresistance of the skin of newborn rats irradiated at 0–6°C. In 1956 Hornsey [12] reported that no mice of the T strain survived longer than 30 days when subjected to 900r of whole-body X-irradiation at normal body-temperatures; but mice irradiated with the same dose at body-temperatures of 1°C, and subsequently resuscitated, all survived. On this and other data, a protective factor of 2·8 was associated with hypothermia of 1°C. This factor is what would be expected if hypothermic radioprotection is in fact due to the associated profound hypoxia. Weiss has carried out detailed work on mice irradiated at body-temperatures of 1°C on the protection afforded to the testes,[13] the spleen,[14] and the hæmopoietic tissues [15] and on fertility in the female.[8] In all instances hypothermia during irradiation, but not after it, was associated with considerable radioprotection. Work on cell-cultures,[16] where hypoxia and hypothermia could be studied independently, suggested that the radioprotection exhibited by hypothermic mammals at 1°C is at least largely due to concomitant profound hypoxia. The results of the work done on the radiosensitivity of mammals at 15°C, while they are still breathing and have a functioning circulatory system, is conflicting. After reviewing the evidence, Weiss [8] concludes that the true protection afforded to mammals irradiated at 15°C is slight compared to the protection obtained at 1°C, and is not readily explicable in terms of the "oxygen-effect".

The techniques of induction of profound hypothermia in the man and the subsequent resuscitation are much more complex than the corresponding techniques in small animals. Nevertheless the experimental work has a bearing on two important clinical possibilities. The first concerns the treatment of disseminated malignant disease by whole-body irradiation. The presence within the tumour bed of highly radioresistant anoxic foci is thought to be an important factor limiting the effectiveness of radiotherapy.[7] Wright and Howard-Flanders [17] suggested that, if patients were made "anoxic" during irradiation, they could withstand a higher dose of X-rays, whereas the sensitivity of the anoxic foci would remain unaltered. Weiss [8 14 18] has suggested that this could be accomplished in practice by irradiating hypothermic patients who could safely be made profoundly hypoxic,

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since their hypothermia would protect them from the dangers of hypoxia without materially altering the radiosensitivity of their tumours. Secondly, in people exposed to ionising irradiations the ill-effects could perhaps be delayed by hypothermia, while bone-marrow infusions or other therapy were being organised.

THE METRIC SYSTEM IN PRACTICE

SLOWLY we are feeling our way towards full application of the metric system. The ultimate replacement of the apothecaries' by the metric system for all pharmaceutical purposes is likely to lead to the adoption of this system for measuring inches, feet, and yards; for length and volume should be as inseparable in our minds as part and parcel, and how can this be so without the same language of measurement?

Yet the adoption of the metric system even in pharmacology (which will become all but obligatory in 1963 when the *British Pharmacopœia* will contain no other notation) is not devoid of difficulties. Two years ago one of our university hospitals—the United Birmingham group—decided to anticipate the *British Pharmacopœia* in this respect. The immediate problem for the standing pharmaceutical committee was to equate the metric with the imperial dosage system and to explain this conversion to staff at all levels. For convenience close approximations were adopted. Thus gr. $^1/_4$, so familiar for morphine, became 15 mg.; and gr. 3, familiar for certain barbiturates, became 200 mg. Conversion tables for solids and fluids were printed on two sides of a small indestructible card convenient in size for both the uniform frock and the waistcoat pocket. No prescription was to be accepted by the hospital pharmacies unless it was set out in the metric system. The changeover was achieved without opposition or complaints—though to those of middle age it is not always easy to think of a dose of morphine as 15 mg., even though 1 g. of sulphonamide causes no difficulty: we have become accustomed to our anomalies. The hospital staff had to decide whether letters to general practitioners should continue to be written in the imperial manner. Most decided to discard this here too; for to do otherwise would be to connive at the dual system that they were attempting to end and would destroy the faith of new graduates.

One consequence has been wholly advantageous: wards are now being equipped with metric measuring-flasks and utensils, thus eliminating an arrangement that was both a source of error and an unwarranted burden on the nursing staff, who previously had had to measure in ounces and pints and convert (without the aid of tables) to millilitres and litres in order to satisfy the demands of an up-to-date consultant. But habit dies hard: at least to one ward sister the bottle of intravenous fluid had always been and still was a pint bottle—why not, since so many around her still spoke of giving a patient *x* pints of saline? She therefore recorded each bottle as 600 ml., not appreciating that each now contained 500 ml.

Unification requires that we shall speak and write in terms of centimetres. This is perhaps rather more difficult: "the last 50 cm. of the small intestine" has a strange ring. Moreover it is hard enough to persuade a medical student to procure any tape measure (the stethoscope, though far more expensive, is bought readily enough because it is a status symbol); and tape measures graded in centimetres, though made, are hard to come by.

CURRENT MEDICAL RESEARCH

WHILE he was demonstrating a particularly abstract invention Edison was asked what possible value it could have. He countered, we are told, with the question: "What is the value of a newborn baby?" The value of many of the projects sponsored by the Medical Research Council is apparent immediately; that of others (as with Edison's baby) less immediately.

Work on interferon comes into the first category; for this substance, found in tissue-cultures after incubation with an inactivated virus, inhibits, in wide-spectrum fashion, the growth of many other viruses. Early enthusiasm about the therapeutic value of such an agent was tempered by the possibility that it might prove intrinsically toxic, antigenic, or much less effective in vivo than in vitro. These possibilities have now been investigated, with results which indicate that interferon may have important clinical applications.

An examination of the plasma-kinins seems to belong to the second group; for the function of these compounds, even in normal physiological processes, is still obscure. They are polypeptides formed from plasma by the action of proteolytic enzymes such as trypsin. In contact with exposed nerve-endings they give rise to severe pain, and when injected intravenously cause a fall of blood-pressure by relaxing the peripheral vessels. They may possibly be responsible for reactive hyperæmia, and for the increased blood-supply to skeletal muscle during exercise. More definite grounds exist for believing that they play a part in the vascular changes which persist for so long in burned skin. The kinins are widely distributed: the urine, sweat, and saliva of many animals have been shown to contain them, and their presence in wasp-venom undoubtedly accounts for much of the pain and swelling resulting from a sting.

The drivers of London's double-decker omnibuses have been found to be some three times more liable to sudden death from heart-failure than the conductors. Further work has been directed towards examining the hypothesis that such a difference was due to the two jobs attracting contrasting somatotypes. Age for age, drivers are larger round the chest than conductors; but study of other occupations suggests that the death-rate from ischæmic heart-disease is commonly higher among sedentary workers. Radio and telegraph operators have a particularly high mortality, postmen a much lower one.

Twelve such items in its programme are described at length in the report of the Council to Parliament. Formerly this intriguing résumé of current research problems was available only to those who purchased the full report, the greater part of which was concerned with administrative matters. Now, however, the articles[1] dealing with these projects are published separately at a modest price. These accounts are so topical in nature, and so catholic in appeal, that they are certain to be widely read.

The title of Dr. EDITH SUMMERSKILL has been gazetted as BARONESS SUMMERSKILL, of Ken Wood, in the County of London.

1. Current Medical Research: a reprint of the articles in the report of the Medical Research Council for 1958–59. H.M. Stationery Office, 1960. 3*s*. 6*d*.

Points of View

THE DOCTOR'S PLACE IN THE PATIENTS' HOSPITAL*

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MANY people are important in hospitals, but the most important are the patients. The people who are responsible for the patients' treatment and care are the doctors, and they too are important, because the patients look to them for everything, and in the end the standards of the hospital depend on the quality of the senior medical staff. It is, therefore, important that doctors should know what they are trying to do and what their place and purpose in the hospital are.

The introduction of the National Health Service in 1948 was the signpost towards the idea of the " patients' hospital ", by which I mean a hospital which is orientated towards patients and towards patients' needs, rather than a hospital that is orientated upwards to some authority. Till then attitudes about the hospital were chaotic. Some people seemed to think that the hospital existed for the treatment of the patient's illness and not for the patient. Thus a mental hospital has never been called a hospital for the " treatment of patients with mental disorders ", but a hospital for the " treatment of mental disorders ". Other people seemed to believe that if the hospital was anybody's it was the doctors'. On this view, the patient never wanted to go into hospital, and once he gets there his only desire is to get out as soon as possible. His influence in the hospital is remote and depends on his small capacity to get his ideas accepted by any member of the staff. Another point of view was that the hospital belonged to the community. Not only was it run and financed by local authorities and ratepayers but many thought that its purpose was to dispose of the community's unwanted people. But all these concepts belong to the past, and the concept of the Patients' Hospital should now become the focal point round which decisions can be made as to policy—as to what should be done by anybody inside the hospital and by anybody outside the hospital, however important or however unimportant he is.

HEALER

The first and most obvious role of the doctor in this situation is traditional. The patients under our care do become physically ill and need to be treated in the same way as people who are not mentally ill. Quite a fair amount of organic physical disease is admitted to a mental hospital, as are cases of mental illness founded on organic changes of brain structure, and these need the traditional diagnosis, treatment, and care. Again, patients with acutely disturbed mental states are in a similar position and need similar medical attitudes and are treated by similar means—sedation, E.C.T., and insulin for example. It is in these spheres of mental illness that the young doctor finds himself most at ease and is most clear as to what he is trying to do. It is, of course, in this traditional role that the doctor can function satisfactorily in a benevolent, authoritarian, and omnipotent manner, where his word is never questioned and his instructions are never doubted for an instant.

But this is only one aspect of his role in a mental hospital. One must always remember that a mental hospital is a place not only for patients to get well in but also a place in which patients are allowed to be ill—sometimes for a very long time. Many are unable to respond to the newer empirical methods of treatment and to these the demand that they should get better is intolerable. The doctor in the mental hospital must not always be doing something in an active way. He must also be able to accept his patients' need to be ill, to support them in their illness, to be patient with them in their illness, and to help them to be patient with their illness. He must also support relatives and nurses in this situation.

Indeed one of the most important problems in psychiatry is the problem of the doctor who feels he must cure his patients. We must teach our doctors that their approach in psychiatry must be an understanding of the patient's situation, and that treatment may or may not come out of this understanding as a side issue.

SUPPORTER

The direct demand that doctors must treat and cure their patients is often insupportable to patients and even intolerable to them, and can be dangerous from other points of view to the doctor and to the patient. It is all right if the patient gratifies the doctor by getting better; this is what the doctor wants, and everybody is happy and there are no problems. But so many of our patients do not gratify their doctors in this way. This may lead to a variety of unsatisfactory consequences. Sometimes the treatment gets more and more vigorous and hectic—for example, leucotomy twice or three times, ill-advised E.C.T. sessions, or rejection to the so-called chronic wards.

In recent years a more dangerous form of rejection has been to discharge the patient and push him out of hospital, often to the acute distress and disharmony of relatives and the environment. Even more recently, there has been a tendency almost to deny the existence of chronic psychosis or chronic mental illness; to behave as if they did not exist; to behave as if they were all the fault of some doctors' attitudes in the past in imagining the existence of chronic psychosis. A similar attitude of rejection is to allow the illness to exist, but to deny that its after-effect is a psychiatric problem. Yet these patients were once acutely ill, their illness has left them crippled mentally, and their state is much the same as that of a man who has had an accident and lost a leg, and whose doctors, having done their part, leave it to somebody else to see how he can best function with one leg.

These forms of rejection are a result of the doctor's personal need to cure patients—to preserve unthreatened his own omnipotent fantasies of being a healer. This need to cure is seldom, if ever, a sublimation; it is nearly always a reaction-formation against underlying destructive needs and wishes, and this is why the need to cure is so dangerous within psychiatry. It does not matter in surgery; but in a mental hospital the patient may never react to what is on top in the doctor, but to what is underneath. Many of our patients will not be in touch with the reaction formation of the doctor's need to cure him, but only in touch with the underlying destructive impulses. From this spring many of the patient's fears. We need, therefore, doctors who, besides accepting their traditional role, are able to accept and be at ease with their own omnipotent

* Based on a paper read, as retiring chairman, to the psychotherapy and social psychiatry section of the Royal Medico-Psychological Association on July 15, 1960.

fantasies; to take over ill patients in a supportive and expectant way, content to provide them with simple things; and to help them to find a solution to their illness in whatever way they are able to go. We must have doctors who can allow patients to be ill.

TEAM LEADER

In recent years there has been a change in the way mental hospitals function—a change best described as the team-approach method as opposed to the old benign authoritarian method. In this everybody works together as members of a team, and difficulties in the team are regarded as impediments to be overcome. In this situation there is a gradual tendency to develop a uniform attitude in all people who come into contact with the patient. This approach leads to a situation in which everyone who is a member of the team is directed towards the patient. The team-approach method provides the doctor with his third, highly important, role as the leader of the team. He is put in this position by the needs of the patients and he is kept there by these needs. He has the job of looking after everybody who is looking after the patient. The tendency within the team is for everybody to help in whatever particular way he can help most. There are no longer rigid distinctions between what is the doctor's job, what is the psychiatric social worker's job, what is the nurse's job, what is the occupational therapist's job. The functions merge and overlap, but the doctor has the task of keeping the team together. Even the youngest and most newly qualified doctor has something to contribute from his own cultural and social background which may be invaluable to the life of the patients: it may be cricket or it may be painting. In this way psychiatrists are beginning to widen the narrow boundaries of professionalism, and are ceasing to be as possessive as they once were towards the patients under their care. They are allowing different people to help their patients. Indeed many doctors wish to enlarge the concept of the team to include everybody who works and lives within the hospital, recognising that the most important therapeutic need of all their patients is other human minds. In the past doctors took the attitude that only people who came under their immediate direction (and this usually meant authoritative direction) could be allowed to have anything to do with their patients. This was the main reason for the artificial division within mental hospitals between the medical and nursing services and the administrative and maintenance services. This division is not compatible with the concept of a patient's hospital, where the patients share in the running of their own hospital, and it is highly desirable that they should be employed and supported in all its departments.

Nobody can work in a mental hospital with an attitude of mind which says that " patients are no concern of mine, that is the job of the doctors and nurses " without being destructive of the total functioning of the hospital. The maintenance of a therapeutic atmosphere within the hospital is the responsibility of all members of the staff and it must certainly be the continual preoccupation of the administrative staff.

I suppose that in mental hospitals there has always been the problem of " patient jealousy ". We may be jealous of our patients because they are allowed to let themselves go, to smash things, to be bad-tempered, and to swear, while the staff have to be good-tempered and self-contained the whole time. Or we may be jealous of the creativeness of some of our patients. Any capacity they have to be normal seems intolerable to many other people because these are patients. In the patients' hospital there is greater scope for jealousy. This attitude is shown by such remarks as " They are looked after too well ", " They get too easy a time ", " Why should they get better while they have got everything they want? " This is one of the problems which face the doctor as leader of the team.

Another is the problem of " nobody tells me anything ". I am not saying for one moment that it does not happen anywhere else but in mental hospitals, because I am quite sure that it does. But I think the difference is that in mental hospitals there is an awareness of this phenomenon. It is true one can talk about it and sum it up in the words " importance of communication ", but this does no more than half-answer our problem. The real answer lies in the relationships within the hospital. Everybody should have a feeling of security and confidence in belonging to a team: " Nobody tells me anything " is essentially an attitude of passivity, possibly with some avoidance of knowledge; because, if one does know, one has to accept the responsibility of knowing and some action may then be needed. " Nobody tells me anything ", though it may be fostered in some mental hospitals, is fundamentally a defence situation of the individual. This defence situation can easily have authoritarian secrecy as its active partner, and the collusion between these two can disappear only by expanding the team more and more.

ADVISER TO THE COMMUNITY

Inside the hospital, therefore, the doctor has three important functions: he is a doctor in the traditional sense, a doctor in the supportive, expectant, and psychotherapeutic sense, and a doctor who is the leader of the team. Outside the hospital he has also to cope with the problem of what the community feels about all this and what the community really wants.

One of the main difficulties is that the community has never known what it does want. It does not want doctors to retain people against their will, but at the same time it demands that doctors should look after and take away from it people it cannot support or cope with and it blames doctors forcibly if they appear dilatory in this task. Naturally, these two demands are contradictory, and the doctor has a very important contribution to make to the community in balancing their claims.

At my own hospital the community seems to be more at ease with us, and with the patients, now that there is much more freedom, and patients are able to come and go more readily. I think this is because their fantasies are not so stirred and reality has come in. In addition, of course, the local community is pleased to have the trade of the patients in their shops; and often they take a compassionate interest in the patients' welfare and get a great deal of satisfaction out of feeling that their contact with the patient does him good, which of course is true. But naturally they complain bitterly if any of the patients behave in any way unsatisfactorily, because they feel " let down " in themselves.

The new Mental Health Act has clearly said that the problem of mental illness cannot be solved by laws and administration, and it lays much of the responsibility for coping with it on the doctors. It therefore behoves us to give the lead as to what the future is to be, and to make up

our minds whether we can run our mental hospitals as patients' hospitals in which some patients can get well, some can remain ill, and some can be cared for over an indefinite period; or whether we really think it would be satisfactory to have small first-class units in general hospitals, and then discharge all who do not respond to treatment to the care or neglect of the community. Are we working towards an improvement of our mental hospitals or towards their dissolution? Is it really satisfactory that we should provide only for those patients who gratify their doctors by getting better quickly, and discharge the rest to the community? Psychiatry has always set an example to all branches of medicine by being willing to look after patients who do not get well—an example which other specialties are now beginning to copy. It would be disastrous if much of our hard-won knowledge and experience were to be dissipated because of some vague feelings in the community about mental hospitals, and because there are beliefs higher up that it will be much cheaper to get rid of mental hospitals. It would be disastrous if the highly desirable development of units in teaching hospitals should lead to the destruction of the mental hospitals.

Today, though many changes are being made, our goals are quite unclear. Their rationale is undefined, but seems to depend on the unconscious need to deny the existence of chronic mental illness, to deny to a certain extent the existence of mental illness altogether, and to pretend that mental hospitals belong to the bad wicked past. Are we in fact by this extraordinary turn of events preparing for a future psychiatric retrogression, in which we have first-class patients in the general hospitals, and second-class and third-class patients somewhere else, more forgotten than they were before? There always have been many schizophrenics who have lived their lives in the community untreated, unknown. Are we really anxious that the number of these people should be steadily increased?

Special Articles

BLOOD-PRESSURE IN RELATION TO AGE AND SEX IN THE TROPICS AND SUBTROPICS

A Review of the Literature and an Investigation in Two Tribes of Brazil Indians

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DURING the past 45 years relatively few papers have been published dealing with blood-pressure measurements in population groups living in the tropics and subtropics. There are, indeed, large areas, such as West Africa, where practically no data are available. As has been shown in previous reviews,[1–3] a comparison of mean blood-pressure in various ethnic groups is subject to many errors and inaccuracies because of differences in method. For this reason, no such comparisons will be made between the various groups covered by the reports reviewed here. Two questions, however, will be considered which are basic to our understanding of the epidemiology of blood-pressure: (1) Does blood-pressure rise with age? (2) Are there any sex differences?

Table I lists 26 references,[4–29] indicating the geographical location of the study, the population group(s) examined, their sex and their age, the type of blood-pressure measured, whether there was a rise with age, and whether the males showed a higher pressure than the females, or vice versa.

All the groups were located between latitudes 30° north and 30° south. There are, however, considerable variations in climatic conditions owing to differences in altitude and humidity.

The groups examined in the Virgin Islands, the San Blas Islands, Ponape and Puka Puka islands, rural Fiji, Formosa (Taipei) and Ceylon form the most representative samples. They comprise, in some instances, between 50 and 90% of the total population (Virgin Islands, rural Fiji); and, where their percentage of the total is smaller, the selection seems to have been carefully done. The poorest samples are those which consist of patients—e.g., the two groups in Puerto Rico and the one in Guatemala—even though the authors state that they excluded all those with cardiovascular-renal diseases. Five out of the twenty-five groups consist of men only. Most groups include all ages from adolescence to old age.

The mean blood-pressures given by the investigators are based on single readings of casual blood-pressure, usually with the subject sitting (except in two series, in which the subjects were lying down); in five groups, they took several readings and recorded the lowest, which was used for their calculations of mean values.

In twelve groups, a significant rise of the mean systolic and diastolic pressures with age was noted in both men and women. In four groups this rise was confined to women; in five, only men were examined. Four groups did not show any rise with age in either sex.

Nine out of a total of twenty groups showed no significant sex differences. In eight groups, women had considerably higher mean pressures than men. The systolic pressures showed a greater mean difference (between 9 and 15 mm. Hg) than the diastolic pressures (between 3 and 8 mm. Hg). With one exception, these differences were not large until after 30–45. Group 2a showed a large difference at 15. In the three groups in

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which men had higher mean pressures than women, the mean differences were smaller—between 5 and 11 mm. Hg for the systolic and between 3 and 6 mm. Hg for the diastolic pressures. These differences, however, remained about the same from 16 to 60–70.

PRESENT SURVEY

During a nutrition survey of two tribes of Brazil Indians in May-June, 1958, I took casual blood-pressures in all adults over 16. Both tribes live in the Amazon basin of tropical Northern Brazil, on the shores of two southern tributaries of the Amazon.

The Mundurucús, who were once great warriors, used to live in a savannah-like forest; but during the past 45 years they moved and settled along the Cururu River, where a Franciscan mission takes care of about two hundred of them in a mission village. The greater acculturation of the Mundurucús is shown by the fact that each family, consisting of husband, wife and children, lives in individual homes, whereas the Carajas still live in large family groups of some 20–30 people in each hut. Seventy-seven, aged 16–60+, representing all adults in the village together with a few others living up river, have been examined. The mean blood-pressure of these seventy-seven is shown in table II.

The Carajas always lived along the Araguaia River. They have been in contact with civilisation for some time, but are still pagans and practise their rites and dances (which are famous) just as in previous times. Eighty-nine Carajas, aged 16–60+, have been examined, representing all in this age-group in their main village, plus a few living in a smaller village about 25 miles down river. Their mean blood-pressures are shown in table III.

The diagrams show comparisons between the mean systolic and diastolic pressures by age for men (fig. 1) and women (fig. 2). There is a significant rise of the systolic and diastolic pressures with age in the Mundurucús men whereas no such rise could be found in the Caraja men. In the females, a similar (but not statistically significant) rise is seen among the Mundurucús, whereas the pressures of the Caraja females remain more or less constant throughout. The men of both tribes have significantly higher systolic pressures than the females, but the diastolic pressures show little difference.

TABLE II—MEAN BLOOD-PRESSURES (mm. Hg) OF MUNDURUCÚS

Age-groups	Systolic pressure		Diastolic pressure	
	Males	Females	Males	Females
16–20	104·7 (*3*)	92·0 (*4*)	66·6	59·2
21–30	117·2 (*10*)	104·3 (*15*)	71·4	64·8
31–40	108·9 (*13*)	109·0 (*10*)	73·4	72·8
41–50	115·5 (*8*)	111·7 (*6*)	73·3	70·7
51–60	132·8 (*5*)	106·7 (*3*)	77·2	70·0
Total	*39*	*38*	..	..

Number in each group in parentheses.

TABLE I—DETAILS OF BLOOD-PRESSURE STUDIES REPORTED IN LITERATURE

Region	Groups and number examined	Sex	Age range	Mean blood-pressure quoted		Rise with age		Blood-pressure higher in		Blood-pressure the same	Authors
				Casual	Lowest	Yes	No	Males	Females		
1. Virgin Islands, U.S.A.	4913 Negroes and whites	M and F	15–80	x		x			x (only Negroes)		Saunder and Bancroft (1942)[4]
2. Puerto Rico	250 patients	M and F	15–60	x		x			x		Ashford and Dowling (1930)[5]
2a. „ „	100 „	M and F	10–80	x		x				x	Torgerson (1930)[6]
3. Bahamas Islands	Negroes, urban and rural ..	M and F	20–64	x		x			x		Moser (1959)[7]
4. San Blas Islands	407 Cuna Indians, rural ..	M and F	16–66+		x		x			x	Kean (1944)[8]
5. New Orleans, U.S.A.	5853 White and Negro workmen	M	18–65	x		x					Adams (1932)[9]
6. Jucatan, Mexico	1066 Mayas and Mestizos	M and F	15–89	x		x			x		Saunders (1933)[10]
7. Guatemala	457 patients, Indian and mixed	M and F	10–70	x		x				x	Shattuck (1937)[11]
8. Ponape Islands, E. Carolines	251 Polynesians	M and F	20–39	x		x(F)	x(M)			x	Murrill (1948)[12]
9. Puka Puka, N. Cook Islands	491 Melanesians	M and F	1–65+	x		x(F)	x(M)			x	Murphy (1955)[13]
10. Fiji Islands	6297 Fijians and E. Indians	M and F	10–70+	x		x			x		Lovell et al. (1960)[14]
11. Australia, Lockhart River	103 Aborigines	M and F	40–70	x			x(?)			x(?)	Nye (1937)[15]
12. New Guinea Coast and Highlands	623 Papuans	M and F	11–60+	x			x		x (Highlands only)		Whyte (1958)[16]
13. Philippine Islands	717 Philippinos, urban ..	M and F	15–90	x		x				x	Concepcion and Bulatao (1916)[17]
14. Formosa (Taipei)	9729 Taiwanese and Chinese, urban	M and F	15–65	x		x				x	Lin et al. (1959)[18]
15. India: W. Bengal and Calcutta	6000 Bihar police officers and firemen	M	18–25		x	x					Dotto (1954)[19]
N.E. Assam	3381 plantation workers ..	M and F	10–74	x		x			x		Wilson (1958)[20]
Agra	4526 Agrans	M and F	1–70	x		x		x			Mathur (1958)[21]
N. Delhi	1134 Urban and rural ..	M and F	10–65	x		x(F)	x(M)	x			Padmavati (1959)[22]
Madras	772 Urban	M	21–50+		x	x					Srikantia et al. (1960)[23]
North and south	10,000 Urban and rural ..	M and F	15–70+	x		x		?	?		Chopra et al. (1942)[24]
16. Ceylon	610 men, 4 groups.. ..	M	30–80	x		x					Gunewardene (1935)[25]
	7000 Ceylonese, mixed groups	M and F	10–50	x		x(F)	x(M)			x(?)	Bibile (1949)[26]
17. Kenya, E. Africa	100 men, 4 tribes	M	15–59	x			x(M)				Donnison (1929)[27]
18. Uganda, E. Africa	394 people, agricultural and pastoral	M and F	16–51(M) 21–40(F)		x		x	x			Williams (1941–42)[28]
19. Kalahari Desert, South Africa	78 bushmen	M and F			x		x		x		Kaminer and Lutz (1960)[29]

DISCUSSION

All those groups which showed no increase of mean blood-pressures with age during adult life represent relatively small homogeneous populations living under primitive conditions in relative isolation, more or less undisturbed by their contacts with civilisation. Many of them still walk either in the nude or in shorts only, and they live almost entirely on the natural foods of their environment. This is also true of the Carajas.

The Mundurucús, though their mean pressures are still low as compared with those of many civilised groups, show a rising trend with age as do all civilised groups. In comparison with the Carajas, the Mundurucús are less primitive; they have been converted to the Catholic faith and their whole way of life has been changed under the influence of the mission. Outwardly they appear happy;

TABLE III—MEAN BLOOD-PRESSURES OF 89 CARAJAS

Age-groups	Systolic pressure		Diastolic pressure	
	Males	Females	Males	Females
16–20	109·5 (*7*)	96·0 (*2*)	72·5	69·0
21–30	109·8 (*9*)	104·1 (*15*)	72·9	70·7
31–40	107·3 (*11*)	105·4 (*10*)	70·5	72·2
41–50	100·9 (*7*)	100·0 (*7*)	69·1	69·4
51–60	109·0 (*6*)	98·0 (*6*)	70·3	67·7
61+	110·3 (*6*)	108·0 (*3*)	69·7	64·7
Total	*46*	*43*	..	..

Number in each group in parentheses.

but what do we know of the inner conflicts between their old animistic beliefs and the new religion? There have been other changes in their life habits—e.g., the regular use of table salt (sodium chloride) instead of plant ashes (potassium chloride) and the use of tobacco.

In both Brazilian tribes, men have higher systolic pressures than women, as was found in two tribes in East Africa, and in the more civilised people in Agra and New Delhi. These differences are not easily accounted for, because in the other primitive groups such differences do not exist. In the East African tribes, and in the Agra and New Delhi people, both systolic and diastolic pressures

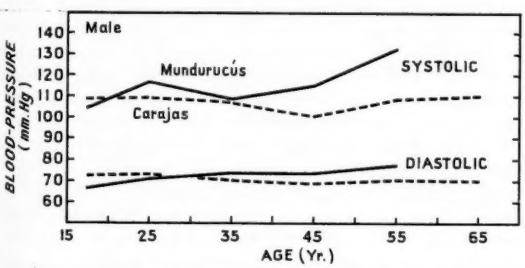

Fig. 1—Relation between blood-pressure and age (men).

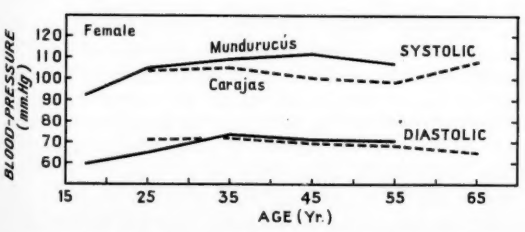

Fig. 2—Relation between blood-pressure and age (women).

are higher in the males; in the Agra groups these differences diminish in the groups over 45. In the groups which show the opposite—i.e., higher systolic and diastolic pressures in the females—these differences become significant only after age 35–40. This might be explained by the endocrine changes in the female with the onset of the menopause. It is now generally accepted that women during active reproductive life are relatively free of atherosclerosis and its severe sequelæ. They seem to be similarly protected against the mechanisms which raise blood-pressure. It remains, however, unexplained why, in some groups, pressures remain lower in women even after the menopause.

That socio-economic conditions have a bearing on rise of pressure with age is shown in the New Delhi study where only in the high-income group was there a significant rise with age, which was also associated with a steady increase in weight. One cannot generalise, however, from the data reviewed on the importance of socio-economic conditions, since the majority of the groups showing a rise of pressure with age belonged to the lower economic strata. Perhaps, under some conditions, the stratification of a population into high and low economic levels causes the less well-off members of a community to become conscious of their poverty and either to feel ashamed or to feel rebellious. Such emotions, rather than poverty itself, may influence blood-pressure levels in the adult. In the groups where there is no rise with age, such consciousness of poverty may not exist, either because these groups represent small, not well differentiated, societies, or because they have accepted poverty without reacting to it in a negative way.

SUMMARY AND CONCLUSIONS

26 references concerned with blood-pressure measurements in various ethnic and social groups living in the tropics and subtropics have been reviewed with respect to two problems: (1) Does mean blood-pressure rise with age during adult life? (2) Are there any sex differences during adult life?

Mean blood-pressures of two tribes of Brazil Indians, living in the tropical Amazon basin of Northern Brazil, are recorded. These pressures are shown to be low throughout adult life; they have a tendency to rise with age in the Mundurucús whereas no such tendency was found in the Carajas. Men showed significantly higher systolic pressures than women in both tribes.

The two tribes differ in their way of life in that the Carajas are more primitive and live more or less as their ancestors did before they had more intimate contact with civilisation. The Mundurucús, on the other hand, have accepted some of the culture of Catholic Brazil.

It is postulated that the rise of blood-pressure with age, observed in the great majority of the groups, is a consequence of civilisation, or rather of the process of acculturation. In order to confirm this hypothesis, however, more group studies of blood-pressure levels in people living at different stages of civilisation are needed. Because of the rapid changes taking place in the developing countries of the world today, the acquisition of such data is a matter of great urgency.

As to sex differences found in those groups, the situation appears less clear. Whereas in most groups men tend to have either lower pressures than women after 35–40, or to have equal pressure levels, in a few groups (including

the two Brazil Indian tribes) the blood-pressure of men was higher even after 35–40. While the higher pressure in women at 35–40 can be explained by the endocrine changes occurring during menopause, the opposite trend remains unexplained. Further group studies of representative samples of both sexes may help to clarify this question.

Particular attention should be given in such studies to differences between various groups in their constitution, diet, and psychology.

Occasional Book

PRISONS INTERMINABLE

RECENT months have seen an astonishing amount of action in and around the subjects of criminal science and penology. New thinking in the Prison Service, more activity among criminologists, and the reorientation of ideas implicit in the Mental Health Act are partly responsible, but these trends themselves surely reflect a long-overdue revolution in thinking—for when " original sin " loses its force as an explanation of all evil more rational (and humanitarian) ideas must take its place. As signs of this revolution a British Academy of Forensic Sciences has lately been formed and, in parallel, a similar though smaller Forensic Science Society; and each has produced a new journal.[1 2] The well-known *British Journal of Delinquency* has widened its scope and changed its name in July to *The British Journal of Criminology*.[3] The Prison Service also has a new journal,[4] intended to complement the existing *Prison Officers' Magazine*, and it also began in July, offering remarkable value for 6*d*. Two successful international congresses on crime were held last year (in London and The Hague); research projects are in hand in various places; and the new Institute of Criminology is making a start with training programmes and research.

For the public, never have there been so many newspaper articles, books, and broadcasts (many of them on a very high level) on crime and prison affairs. Some material—the biographical accounts of the more unpleasant murderers, for example—still supplies vicarious satisfaction for perverted appetites, but there are signs of a maturer sense of responsibility among many publishers. The favourable reception by all but one of the national daily newspapers of the report on corporal punishment [5] is another indication of the trend of opinion. Particularly welcome are two valuable books by eminent penal reformers published within weeks of each other; *The English Prisons* [6] by D. L. Howard offers a broad survey of penal matters with particular reference to their historic evolution; and Hugh J. Klare tackles the detailed structure and function of the prison system in his aptly named *Anatomy of Prison*.[7]

Mr. Howard's book has the widest interest: in its first three-quarters he has done for the prisons what Kathleen Jones did for the mental hospitals—given a clear, accurate, and often gripping account of the appalling history of penal methods from bridewells via hulks and deportation to the present day. The parallel of penal with lunacy reform is interesting but not unexpected: the early 19th century saw the fruition of John Howard, Jeremy Bentham, and Elizabeth Fry's work in the large prison at Millbank, which offered, for the first time, reasonable conditions of life. It was the first prison to appoint, in 1816, a regular governor, medical officer, chaplain, master manufacturer, and, above all, a lady matron (one of several innovations, this, of which the current wave of reform still falls short). Notwithstanding the occasionally odd idea of Bentham (especially in prison design), the Millbank regime at its best offered creative personal relationships with staff and good occupational therapy—though this did not last long.

A riot, scurvy, dysentery, and cholera led to changes of staff. The spread of the treadmill accompanied a hardening of opinion, and the 1839 Act brought the American technique of total isolation to this country: prisoners exercised masked, their cell windows were blocked out, and they were even screened from sight of the chaplain during religious services. In almost complete sensory deprivation, the convict was expected to meditate on his sins, free from the contamination of his colleagues.

Nevertheless Pentonville, where solitary confinement began, did offer hot and cold taps and a water-closet in the cells—luxuries long since removed. It is interesting to compare present reluctance to use prison labour for public works with some past policies which regarded this as a cornerstone of penal treatment, if a crumbling one. Until the 1877 Act placed prisons under central control, facilities were very uneven. At best there were such people as Captain Maconochie whose interesting " marks system " never had a fair trial; he opposed time sentences on grounds which are as firm now as in 1846, and he wanted to impose punishment by a certain number of marks, to be reduced at a maximum of, say, 10 per day subject to the convict's industry and cooperation.

On the current scene Mr. Howard is trenchant enough and rather concise, but Mr. Klare's book more than makes this good. His careful, sometimes pedestrian descriptions of the prison community and the functions of the various staff members are very fair and give a clear unemotional view of what goes on. He is particularly sympathetic towards the problems faced by prison officers in implanting new and less restrictive methods; and he believes that these should come gradually. But something is lacking in his discussion of group methods, though he is right to point out that group discussions, however often they are called " counselling ",[8] must become " insight " psychotherapy to do much lasting good. He appreciates too that something more than common-sense is needed to understand and help the antisocial—though he does not face the difficult inter-professional issues involved. Both books say stern things about the promotion system and prospects within the service, both of discipline staff and of governors—and similar remarks could relate to the few prison doctors. Both books, again, are sound on future design and criticise the structures in course of erection here: Klare calls for prisons of smaller size containing within them many small units of a dozen or so men.

But many of these comments—like those about the number of men to put in a dormitory or the way to pro-

1. *Medicine, Science and the Law*. The official journal of the British Academy of Forensic Sciences, c/o 11, New Fetter Lane, London, E.C.4. Published quarterly, £3 3*s*. a year. See *Lancet*, Dec. 17, 1960, p. 1338.
2. *Journal of the Forensic Science Society*, c/o Rossett Holt, Pannal Ash Road, Harrogate, Yorks. Published twice yearly, £2 a year.
3. *The British Journal of Criminology*. Published quarterly by the Institute for the Study and Treatment of Delinquents, 8, Bourdon Street, London, W.1. £2 2*s*. a year to non-members.
4. *Prison Service Journal*. Edited in the H.M. Prison Service Staff College, Wakefield. H.M. Stationery Office. Published twice yearly. 6*d*.
5. See *Lancet*, 1960, ii, 1177.
6. The English Prisons: Their Past and Their Future. By D. L. HOWARD. London: Methuen. 1960. Pp. 174. 21*s*.
7. Anatomy of Prison. By HUGH J. KLARE, Secretary of the Howard League for Penal Reform. London: Hutchinson. 1960. Pp. 160. 18*s*.
8. See *Lancet*, 1959, ii, 1015.

mote an assistant governor—are what one might call micro-reform. Again, calls for more staff, better pay, and new buildings, though very necessary, are not exactly new, nor likely to excite much argument. The authors are to be commended for their care, on the whole, not to throw ideas about without knowledge of the circumstances or reflection upon their consequences. But many readers will begin to wonder where present-day penal reformers are going.

To describe Mr. Klare and Mr. Howard as " rebels without a cause " is to do them less than justice, but the books do highlight the puzzling position in which high-minded laymen now find themselves. Reform has traditionally stemmed from the pressures of concerned bodies (such as the Howard League) upon a tardy administration, and from mobilisation of public opinion. Now, however, the Prison Commission must be regarded as ahead of the Government front bench, which in turn is some years ahead of the public (and, seemingly, of the Opposition) and a century or so in advance of its own back bench. The Commissioners' readiness to try out new ideas and methods is almost startling, and the changes which they seek are moving as fast as their own staff problems, Government finance, and the public attitude permit. Concerning reform it seems sad that these two books have little more to add to the Prison Commission's work than " Amen ". It is the public, these days, that need reforming, for without a change in attitude, administrative improvements are held up at every turn. This is not to say, unfortunately, that penal reformers might as well put up their shutters. Plenty still needs to be done, in prevention especially, and this could be the penal reform of the future, for the prevention of crime depends on understanding its cause, and this involves scientific discipline, funds, and a good deal more interference in people's lives and in the judicial process than has yet been possible.

Then there are the courts themselves which, as fact-finding bodies, are long overdue for critical re-examination: the limitations of the 12 good men and true, over some complex technical issues, have long been evident, and inter-court comparisons of sentencing policy show alarming discrepancies. The efficiency of a court of law in terms of time, effort, and accuracy is wide open to scientific study. Changes in juror attitude during the various stages of trial, inter-jury reliability, the influence of personality factors in judge and counsel, and the capacity to discern the truth could all be studied in vitro or—granted a very sweeping change in attitude—even in vivo. Clearly this calls for the capacity to look objectively at the legal process, and perhaps we have too long believed our present system to be a model for the world. Justice for the individual ought to be enhanced by clearer knowledge of all the facts, and if anyone is likely to suffer from—or to obstruct—such study, it would be the lawyers: their training and orientation, based on precedent and ancient law, is the least designed to encourage a forward-looking reformative approach to their discipline. The competition in legal dialectics between counsel may not, after all, offer the most effective way of detecting the wicked and of protecting the innocent from wrongful conviction.

Penal reformers might look at their province more widely if their function is to have the impact in this century which it had in the last.

RICHARD FOX
M.B., M.R.C.P., D.P.M.

In England Now

A Running Commentary by Peripatetic Correspondents

SEVEN years have winged away since I interrupted this column's contemplation of flying saucers with my brash story of seeing a Golden Eagle in the Lake District.[1] Our pathologist was a keen bird-watcher: he took me on one side and explained in a kindly tone that it could have been nothing more than an outsize buzzard. Other people were not so tactful. For seven years I have brooded with a sense of injustice, sobbed into my pillow at the subconscious level, clenched my knuckles over the steering wheel every time we passed the tree where the eagle once perched. Or was it a buzzard? Nothing but wild horses or mescalin would have dragged the word eagle again from my lips.

And then one Sunday afternoon last summer I was flattened out in a deck chair on the lawn. The sun was warm and the roast beef had been rare and tender. Through the haze of drowsiness came the familiar mewing of buzzards. They often ride the thermals over Troutbeck, their plaintive call soothing to friendly ears. But a sharper stranger cry came through. I held up my hand against the sun and opened one eye. Five buzzards were wheeling in silhouette a thousand feet above, wheeling with purposeful turns and climbs and dives. One was much bigger than the other four, and it seemed to be the target for attack. Away they curved over the ridge to Kentmere. I yawned and shut out the deep blue sky. What should I care about outsize buzzards? Maybe someone had been sticking aquiline D.N.A. into the peritoneal cavity of some luckless buzzard chick. Maybe it was just another circulating bird of passage evolved from a Pekin duck. It would never surprise me where they could make a bird fly nowadays. Anyway, ours had flown out of sight too.

The afternoon grew warmer: I floated in and out of the border of dreams. How was I to know if the fifth buzzard had accidently slipstreamed its thymine in front of its cytosine? It could have had a straight flush of aminoacids and won the jack pot: the new biophysics has long passed me clueless by the way. I tried another tack. What would be the effect on the cubic capacity of a buzzard if the number of consecutive simple fissions of its egg cell should happen to go on once too many times? Mental arithmetic was never much good, and 10^{10} is a bit of a strain on a Sunday afternoon. Anyway, even if the fifth bird's coding had been tampered with, who was I to criticise its genetic eccentricities? Our Lake District has a traditional flair for sheltering eccentrics: paradoxically, the more eccentric they are, the more centripetal is their distribution: at least to the point of mutual repulsion. Maybe it gives them more scope to fly off at a tangent. I decided to let the other four buzzards chase up their own eugenics: outsize freaks have brought nothing but sorrow to me.

Last month a tidy great bird was found dead in a trap. It was a Golden Eagle. When I saw it in the museum it gave me a broad wink with its new glass eye After seven years in the wilderness I am beginning to raise my head again.

* * *

One of the first physiological facts I grasped, no doubt like thousands of other not very earnest students, was that a gentleman named His had given his name to posterity attached to a bundle. Since then I have never lost hope that I might come across the other half of what is now a famous pair, and at last, in a footnote to one of your leaders, I have found it—Hers, H. G. *Rev. int. Hepatol.* 1959, **9**, 35. What a pity that they couldn't have published a paper together. His and Hers!

* * *

When we moved house the family went on ahead while I drove a heavily laden car rather slowly across Canada. Having once before driven over the somewhat unexciting main route through Montreal, I decided to try the country route which seemed to be more direct and would be a change. Certainly it was direct enough, but the wise people of Quebec do not build motels where there are no tourists. So that just

1. *Lancet*, 1954, i, 674.

before midnight I found myself looking for some place to stay. Eventually in a small village I was told that a pension "found itself just opposite to the garage up the street". I checked in with some relief. The place was gloomy but clean, as were the two old ladies who appeared to have come from a local performance of *Arsenic and Old Lace* to supervise the registration ceremony. There was a vaguely familiar smell about the whole place, rather like the cedarwood crayons I used to buy as a child. On my return from the car with my bags, the odd perfume was explained, for I was faced by a notice which I had not previously seen, "Pension de St. Émile", and underneath in smaller letters, "M. Jacques Leroux, Directeur des Funéraux". The decorations were in keeping with the rather specialised nature of the house, except in the bathroom. Here, over a geyser of great antiquity, some humorous guest had pinned a picture of a most charming though not overdressed young lady. I can only presume that the old ladies did not often use this bathroom. I never did see M. Leroux.

* * *

An outpatient, one of our regulars, started to tell me about some new trouble which I felt could legitimately be fobbed off on to her long-suffering G.P. "Have you told your own doctor about it?" I asked hopefully. "Well no, doctor, the truth is that I have been feeling too ill to do anything like that, but now that I'm feeling better I think I might pop round and tell him all about it."

* * *

In an appendix to *The Organization Man*, William H. Whyte tells the aspirant How to Cheat on Personality Tests. Mr. Whyte is unfair to himself because the measures he suggests are not "cheating" but "do-it-yourself brainwashing". For instance, when uncertain about an answer he recommends: "give the most conventional run-of-the-mill, pedestrian answer possible. . . . To settle on the most beneficial answer to any question, repeat to yourself:

(*a*) I loved my father and my mother, but my father a little bit more.
(*b*) I like things pretty well the way they are.
(*c*) I never worry much about anything.
(*d*) I don't care for books or music much.
(*e*) I love my wife and children.
(*f*) I don't let them get in the way of company work.

Now, of course, in British medicine we do not have tests of aptitude, promise or ability. Instead we have the membership. As long as I accepted Mr. Whyte's recommendations as "cheating" I did not appreciate their value because who would consider "cheating" the censors? But brainwashing is permissible, provided we call it "cultivating the right state of mind". I accordingly adopted Mr. Whyte's first recommendation without alteration and slightly modified the rest of his technique. As I now have the membership, I feel others who still want it may find it helpful to repeat:

(*a*) I loved my anatomy and physiology, but my anatomy a little bit more.
(*b*) I like medicine pretty well the way it was.
(*c*) I don't worry much about recent developments, particularly American ones.
(*d*) I don't care for books or journals much. It's experience that matters.
(e) I like a little biochemistry, a few X-rays, and an occasional blood-count.
(*f*) I don't let them influence my clinical judgment.

* * *

He was a sprightly octogenarian who had been admitted during the night with retention due to an enlarged prostate. The surgeon, with retinue, was doing his Saturday morning ward round. The cause of the trouble and proposed course of treatment was explained to the old man but he refused all operative treatment and announced that he was going home—catheter and all. He would give no reason but said he might come back "after Monday". When the vanquished surgeon, registrar, and houseman had left the ward he confided to a sympathetic nurse that he was "due to be married on Monday".

Letters to the Editor

PAYING FOR THE N.H.S.

SIR,—The charge for prescriptions has always fallen unfairly on the skin patient, who frequently requires several items.

For example, a patient with seborrhœic dermatitis—a not uncommon condition—may need a shampoo and a lotion for dandruff, a lotion to bathe the skin, a cream to apply to the rash, a lotion for associated intertrigo, vitamin-B tablets with a restricted diet, perhaps an alkaline mixture to balance the acidosis of the condition, and often, during the acute phase of an attack, a sedative.

The prescription sheet may list:

Soap Spirit, B.P.C.
Salicylic Acid and Mercuric Chloride Lotion, B.P.C.
Potassium Permanganate Solution, 1 in 10,000.
Ichthammol Cream.
Calamine Lotion with 1% Ichthammol.
Strong Aneurine Compound Tablets, B.N.F., 2 t.d.s.
Phenobarbitone Tablets, 32·5 mg. (gr. $^1/_2$) b.d.
Alkaline Mixture 14 ml. ($^1/_2$ fl. oz.) t.d.s.

Nothing proprietary or expensive and yet, under the new regulations of 2*s*. an item, the patient will be asked to pay 16*s*. for his "free for all" health service; and many seborrhœics have to continue treatment indefinitely.

If we must accept a charge for medicines, it would be less unfair to the patient at his time of need if the agreed charge were for one week's supply, irrespective of the number of items required; and many of us would feel that a shilling a week is enough to ask a person to pay back out of his sick benefit.

DAVID ERSKINE.

EPILEPSY AND TELEVISION

SIR,—Dr. Mawdsley, and Dr. Pallis and Dr. Louis (Jan. 28), have done a very useful service in drawing attention to epileptic attacks precipitated by watching television. This was discussed at a meeting of the E.E.G. Society on Jan. 14, 1961, at which Dr. L. S. Lange presented an interesting paper from The National Hospital, Queen Square, giving details of 14 cases. Although I have not done any original work on this subject, I have seen several such cases in a neurological clinic over the past three years; and all of them, as expected, showed paroxysmal E.E.G. abnormality on intermittent photic stimulation. Other points of interest are as follows:

(1) Epileptic attacks are not uncommon whilst watching television, but probably rarer whilst watching cinema performances.

(2) Attacks seem more frequent whilst adjusting the controls; each of Dr. Mawdsley's 3 cases and 1 of Dr. Pallis's had a fit whilst so doing; I have noted it in my personal cases; and Dr. Lange stated that "almost all the attacks occurred while the patients were adjusting, or getting up to adjust, the set because of a slipping picture". Professor Gastaut in Marseilles some time ago investigated this finding, enlisting the aid of the television manufacturers.

(3) The frequency range of the flicker-rate and the intensity of the light stimulus are, of course, important factors in precipitation, and both Dr. Cobb at the National Hospital and Dr. Grey Walter in Bristol have made observations on these variables. This may be, as Dr. Pallis and Dr. Louis have shown, because the epileptogenic flicker-rate is in the 18–20 f.p.s. range and, I understand, maximal around 20 f.p.s.

(4) Auditory stimulation may play an additional role in precipitating attacks, and in one of my cases there may have been double stimulation. Auditory stimulation should also be investigated with reference to (*a*) the frequency range of stimuli; (*b*) the on-off effect, whether the stimulation is intermittent or continuous, repetitive or variable.

(5) Finally, whether or not the emotional impact of the scene viewed or the sound heard plays any part in precipitating attacks.

These cases are well known to neurologists but perhaps not so familiar to family practitioners and the general public; when further light is thrown on the subject perhaps the television experts might be persuaded to remove the offending stimuli!

The London Hospital, London, E.1. M. FISCHER-WILLIAMS.

SIR,—I read with interest the articles by Dr. Mawdsley, and by Dr. Pallis and Dr. Louis. I have subsequently seen a sixteen-year-old boy who had a severe grand-mal type seizure while watching television.

His mother said the screen was very bright at the time, and the picture flickered for a few seconds before he had the attack. He was sitting about 3 ft. from the screen.

The boy is known to have been epileptic since the age of twelve, but he has never had a typical grand-mal seizure before. All his previous epileptic attacks were minor affairs with a few minutes unconsciousness and no clonic contractions.

He has been relatively free from attacks while taking phenobarbitone gr. $^1/_2$ twice daily. His mother told me that in the past two years he has had only 3 other epileptic attacks—all of them while watching television. These were slight attacks and he recovered in a few minutes, so a doctor was not called. She does not remember if the picture was flickering or not; but on each occasion he was sitting less than 3 ft. from the screen.

Oswestry, Shropshire. T. B. MADDEN.

SIR,—I was interested in the articles by Dr. Pallis and Dr. Louis, and by Dr. Mawdsley. I wonder if the condition is as rare as the former authors suggest.

Within the past 12 months I have seen in a general pædiatric clinic 2 children who had major epileptic fits when, and only when, they were watching television. I had assumed these were due to flicker from the picture, although this assumption is perhaps rather facile in the absence of E.E.G. confirmation. For some time I have tentatively advised that children recovering from one of the acute infectious diseases, which may be associated with encephalitis, should not watch television during the danger period.

Dr. Mawdsley recommends either primidone, or phenobarbitone with sodium phenytoin for these unfortunates. I suggested to the parents that as television seemed to precipitate seizures it would be better for their children not to watch it. This, of course, provoked expressions of incredulous horror, and perhaps in these days the suggestion is both impracticable and absurd.

Manor Hospital, Walsall, Staffordshire. J. M. GARVIE.

PEMPIDINE

SIR,—We are surprised that Dr. Dollery (Feb. 11) should have misunderstood our paper and we regret if we did not express ourselves with sufficient clarity. We have no doubt whatsoever as to the value of ganglion-blocking drugs and for the past 12 years have used them continuously, and with considerable success, for the treatment of patients with severe hypertensive disease. In fact, our experience is essentially similar to that of Dr. Dollery and his colleagues and we are in agreement with all the views in his letter.

What we had tried to explain was that our experience suggested there was so little to choose between the ganglion-blocking drugs at present available that a controlled trial as to relative efficacy was not justifiable. Such double-blind trials are irksome to patient and doctor, and since the response to treatment is usually good the underlying condition becomes modified during the course of the trial.

Actually, for the past year or two we have used pempidine as the ganglion-blocking drug of choice because it has no relevant disadvantages and certain theoretical advantages over mecamylamine and other compounds. For patients with malignant hypertension we still advise a combination of pempidine and chlorothiazide, not yet being convinced, after 12 months' experience, of the superiority of guanethidine in severely afflicted individuals in whom control of the blood-pressure is urgent.

ARTHUR KITCHIN
CLIFTON LOWTHER
RICHARD TURNER.
Department of Medicine, University of Edinburgh.

SURGEON AND ENGINEER

SIR,—One of the results of the change in the nature of medical practice since the introduction of the National Health Service has been the attraction to appointments in the medical and surgical industries of clinically experienced doctors.

Your annotation (Feb. 11) must have echoed the thoughts of many, like myself, thus engaged in industry and frequently acting as a liaison between their colleagues in clinical practice and the facilities available in their particular industrial sphere.

An organisation aimed at cooperation on the problems of surgical technology, as suggested in your annotation, should be welcomed by all concerned. The nucleus already exists for this, in the form of much experience in various technological fields, both among medically qualified members of medical industrial organisations and among active clinicians who themselves have engineering experience and qualifications.

If some existing central body would sponsor such a project, even if only to act as a secretariat, I think it would be easy to find individuals both willing and qualified to initiate a cooperative venture of this kind.

Hythe, Kent. D. E. STEELE.

STERILISATION

SIR,—May I hasten to assure Dr. Stark Murray and Dr. Talbot (Feb. 4) that I do not believe and have never suggested that " sterilisation of materials was a problem only of operating-theatres and that it might continue to be done in the basement ". In my address at the Newcastle symposium, and in your very clear report of it (Jan. 28), there is nothing remotely suggesting the unlikely view that they attribute to me.

The subject of my address was not the organisation of sterilising services. If it had been I certainly would have expressed views similar to their own, on the very great advantages of central sterilisation. We must, however, face the fact that many sterilisers are still in operating-theatres and in hospital basements. I therefore made the plea—and repeat it here—that even before they are replaced by central sterilising units, someone must be responsible for them. Moreover, I repeat my opinion that when sterilisation of surgical supplies is done in the theatre suite and by theatre staff, the surgeon is usually the most suitable person to be responsible for it. But, as I said in Newcastle (and as you reported) management of a central sterilising department is another matter. On this, Dr. Murray's views have much to commend them. It may, indeed, usually turn out that the most suitable person to direct the central sterilisation department is the hospital pathologist. But we shall be wise to look for the required qualities—technical, administrative, and personal—in nurses, surgeons, engineers, and pharmacists, as well as in pathologists. This is a more intelligent approach than excluding a natural enthusiast from the job and rigidly " writing it into the contract of the laboratory team ". One of the best central sterilisation departments I have yet visited was conceived, developed, and run by a surgeon.

Public Health Laboratory Service, Middlesbrough, Yorkshire. ROBERT BLOWERS.

DIURETICS

SIR,—Your annotation on diuretics (Dec. 17) mentions the trial of chlorothiazide and a " palatable and effervescent " tablet composed of a mixture of potassium salts.

Excessive potassium loss during chlorothiazide therapy, witnessed in patients with refractory œdema, is indicative in most cases of hyperaldosteronism or, in the minority, the result of an inhibition of potassium reabsorption by the proximal tubules. Little conservation of supplemental potassium would be anticipated under these circumstances, and, indeed, this is reflected, in balance studies, by an almost quantitative increment of urinary potassium.

This situation thus demands the combined use of chlorothiazide and spironolactone, which must be given intermittently following mobilisation of œdema to avoid features of hypoadrenal function. When potassium loss is not excessive, chlorothiazide, intermittently and alone, may suffice.

Harrow. J. PICTON THOMAS.

ACUTE INTUSSUSCEPTION IN CHILDHOOD

SIR,—Recurrent and multiple intussusceptions form an interesting group; and Mr. Hadfield's 3 cases (Jan. 21) are remarkable not only in the number of intussusceptions which he found at operation—25 in all—but the fact that he saw all 3 children within the short space of four weeks.

Prof. Robert Gross [1] mentions 1% of multiple intussusceptions in 702 cases, but does not comment further. He also writes: " The largest number of recurrences ever reported in one individual was a child who required 4 operations."

In this connection the following case is of interest:

A boy born on Sept. 12, 1955, and under the care of Dr. M. C. Mair was referred to Paddington Green Children's Hospital, where he was treated by my colleagues, Dr. J. J. Stevenson and Mr. F. W. M. Pratt, and myself.

Three months.—Ileoileocæcal intussusception. Reduced at operation (M. H. H.).

Seven months.—Ileocæcal intussusception. Seen on screening and reduced by barium enema (J. J. S.).

Twelve months.—Admitted with abdominal pain, vomiting, and melæna. Tumour palpable in right iliac fossa, reduced by massage.

Sixteen months.—Intussusception partially reduced by barium enema (J. J. S.). At operation, an ileocæcal intussusception was reduced with difficulty, and 6 ileoileal intussusceptions were observed, the highest almost at the duodenojejunal flexure. All were easily reduced (M. H. H.).

Two-and-a-quarter years.—Barium enema failed to reduce an ileoileocæcal mass (J. J. S.), and the child therefore required a third operation (M. H. H.). This time 2 intussusceptions were found. Prevention of further attacks now seemed imperative. Gross writes, and emphasises his view in italics: " It is not desirable to undertake procedures which are designed to prevent return of intussusception. The chances of a second attack are so small that there is little justification for performing additional operative steps in a critically ill child." But he adds: " For those children who have three, four, or five attacks . . . intussusception is generally caused by a very prominent lip of redundant mucosa at the ileocæcal valve: this projects into the lumen of the cæcum and acts as a leading point. Removal of this is very effective in preventing recurrence: this is most easily accomplished by resection of the terminal ileum and cæcum." I therefore wrote to Mr. (now Sir) Denis Browne asking his advice. He replied that he himself had not come across such a case, and knew of no means of preventing further attacks.

Three-and-a-half years.—Intussusception located in transverse colon. Reduced to ileocæcal valve by barium enema (J. J. S.), but no further. At operation (M. H. H.) it was found to have reduced itself. Appendicectomy performed. It was agreed that the child should have no further radiation, even though an image amplifier had been used on the last 3 occasions.

Four years.—Ileocæcal intussusception at splenic flexure reduced by operation (F. W. M. P.). Six weeks later, following 2 further attacks of pain, vomiting, and melæna of brief duration, right hemicolectomy performed (M. H. H.). The specimen showed an intussusception of the terminal ileum projecting 2 cm. into the cæcum.

Four-and-a-half years.—2 further attacks of pain, which the boy's grandmother (by now an expert in this condition) diagnosed as intussusception. Both settled with conservative measures.

The boy has had no further trouble for over nine months; he is now nearly five-and-a-half years old—a well-developed, cheerful, and handsome boy. In a total of 11 attacks, he has had 14 certain intussusceptions and may have had 19. He has survived 6 operations. His abdomen bears 2 soundly healed scars. Whether he has been treated in the best manner by his doctors may be a matter of opinion, but no-one can doubt that he is a tribute to the skill of the nurses at Paddington Green Children's Hospital.

London, S.W.7. MICHAEL H. HARMER.

P.S.—The very day the proof of this letter was returned to you, Sir, the child attended with a further attack. *Sic erat in fatis.*[2]

TRANQUILLISERS IN PSYCHIATRY

SIR,—Dr. Janssen (Jan. 14) is quite right in calling attention to haloperidol, which is certainly one of the most active psychopharmacological drugs.

In our neurological department we tried the drug in various *neurotic* (non-psychotic) conditions. The results were very satisfactory. Even if phenothiazines and other sedatives had had no effect on the neurosis we achieved excellent results with small doses of haloperidol. Its advantages are that a small dose produces no side-effects and it is absolutely tasteless—valuable assets in the treatment of sensitive neurotic patients.

István Hospital,
Budapest, Hungary. T. LEHOCZKY.

RESEARCH IN GENERAL PRACTICE

SIR,—Many general practitioners in this country and in the Commonwealth are undertaking research of very varied types. We should like to make it known that the committee for research in general practice of the Medical Research Council and the research committee of council of the College of General Practitioners are able and willing to help in a number of different ways:

(1) On the committees there are people who can give advice on the approach to general-practitioner research problems and the techniques which can most usefully be applied to their solution.

(2) General practitioners often require specialised advice on specific aspects of their problems. It is usually possible for us to obtain this help and advice for them.

(3) Some problems require for their solution access to elaborate machinery which can be gained through contact with university, hospital, or other departments. Our committees can help by effecting the appropriate introductions.

(4) A doctor may be working alone on a problem unaware that other practitioners in other parts of the country are tackling the same or related problems. Our committees provide an effective link between interested general practitioners.

(5) It sometimes happens that a promising research project is hampered for financial reasons. Applications for financial help may be favourably received. Grants may be provided for out of pocket expenses, for example, in the employment of

1. Gross, R. E. The Surgery of Infancy and Childhood. Philadelphia, 1953.

2. Ovid. *Fasti*, book I, line 481.

secretarial help or in the purchase of special equipment, and possibly for the provision of a locum tenens. Each application is considered on its merits and on its particular requirements. A doctor wishing for help should give a great deal of thought to his problem and to the practicability of the proposed research before making the application.

Close liaison will be maintained between the two committees so that if an application to the one seems to be more appropriate to the other it will, with the permission of the applicant, be passed on.

Interested general practitioners should communicate with one of the undersigned.

38, Old Queen Street, London, S.W.1. R. E. HOPE-SIMPSON
Secretary, Medical Research Council Committee for Research in General Practice

41, Cadogan Gardens, Sloane Square, London, S.W.3. R. J. F. H. PINSENT
Chairman, Research Committee of Council of the College of General Practitioners.

DIASTOLIC BLOOD-PRESSURE

SIR,—May I support the plea of Dr. Ball (Feb. 11) for an authoritative ruling on the recording of diastolic blood-pressure? I had been taught to record the diastolic pressure when the sound changes in its intensity and this seemed quite correct when, on rare occasions, muffled sounds are heard to persist down to zero!

Torpoint, Cornwall. P. J. BANFIELD.

FORMIMINOGLUTAMIC-ACID DETERMINATION

SIR,—Since we last wrote about the detection of formiminoglutamic acid (FIGLU) by high-voltage electrophoresis [1] we have had considerable further experience, and we have compared a variety of methods. We were therefore very interested to see the letter from Dr. Kohn and his colleagues.[2]

We have found electrophoresis on cellulose acetate to be 5–10 times less sensitive than high-voltage electrophoresis. On retesting some of our known positive urines we found about half of them gave equivocal results. But we should emphasise that our collection-time was different because we collected urine from 0–6 hours after histidine, whereas they collected urine from 3–8 hours. We have shown [3] that peak excretion of FIGLU occurs between 5 and 10 hours, and that very little appears in the first 2 hours. When we collected during the peak excretion time [1] we were able to detect FIGLU in a few normal subjects using high-voltage electrophoresis; so it may well be that the lesser sensitivity of the cellulose-acetate method is sufficient for practical purposes if urine is collected then. We do not think it is if urine is collected for the first 6 hours, because running on cellulose acetate for 30 minutes means that FIGLU is not separated from glutamic acid and identification depends on the different intensities of spots before and after treatment with ammonia. (Ammonia converts FIGLU to glutamic acid which stains well with ninhydrin, whereas FIGLU alone does not.) In a strongly positive urine the ratio of FIGLU to glutamic acid is high, but in the more weakly positive urines it is much lower, so that the differences in intensity are much less marked. If the urine is run for 2 hours on cellulose acetate, good separation occurs; but this results in considerable weakening of the spots, and less than half the above urines gave positive results.

We have also tried to separate FIGLU by one-dimensional paper chromatography. On the whole the results are unsatisfactory and rather less than half of our known positive urines could be detected by this method.

We hope to publish this work shortly.

Medical Unit, University College Hospital Medical School, London, W.C.1. J. P. KNOWLES.

1. Knowles, J. P., Prankerd, T. A. J., Westall, R. G. *Lancet*, 1960, ii, 347.
2. Kohn, J., Mollin, D. L., Rosenbach, L. M. *ibid.* Jan. 14, 1961, p. 112.
3. Unpublished observations.

ATHEROSCLEROSIS AND CORONARY THROMBOSIS

SIR,—Following the publication by Professor Crawford and his colleagues (Jan. 28) of their data on the incidence of coronary thrombosis and severity of atherosclerosis in sudden death from myocardial ischæmia, there can now be little doubt that the pattern of heart-disease differs in younger men, although the authors themselves subscribe to the opposite view.

As is shown in the accompanying table, the figures of which are taken from their paper, coronary thrombosis and myocardial infarction is more frequent, and confluent atherosclerosis less frequent, in younger than in older men. If their data had included men in still older age-groups (60–80) the difference might have been even more striking. It is certainly the experience of one of us (G. A. G.) that coronary thrombosis is rare in this group of patients. Their results support the view that ischæmic heart-disease in young men is chiefly due to coronary thrombosis, whilst in older subjects cardiac damage is due to the silting up of the fine branches of the coronary arteries—a view already expressed in this journal.[1 2]

INCIDENCE OF THROMBOSIS, CONFLUENT ATHEROSCLEROSIS, AND INFARCTS IN MEN WITH MYOCARDIAL ISCHÆMIA (25 CASES PER GROUP)

—	Age-group (yr.)		
	Under 40	40–49	50–59
Recent thrombosis (no. of arteries) ..	18	11	10
Confluent atherosclerosis (mean extent, cm.)	13·2	14·8	15·3
Infarcts (total no.)	13	8	3

Professor Crawford et al. state: "We found nothing to support the suggestion of Gresham and Howard,[3 4] on the basis of dietetic experiments in rats, that coronary thrombosis can occur in the absence of atherosclerotic plaques." We did not intend to imply that atherosclerosis played no part in the causation of ischæmic heart-disease in man. As was pointed out by Yater et al.[5] several years ago, and now confirmed by Crawford et al., most cases of ischæmic heart-disease are accompanied by quite severe stenosis of the coronary arteries. There is strong evidence from the latter authors, however, that there is also an increased tendency to thrombosis not directly related to atherosclerosis. The significance of our animal studies was that thrombosis can occur independently of atherosclerosis in a coronary artery. One would expect, however, that thrombosis is likely to occur more readily at the site of an atherosclerotic plaque where the artery is stenosed. But this does not necessarily imply that the atherosclerotic plaque was the immediate cause of thrombosis. The view could equally well be taken that the blood is in a hypercoagulable state.

Recent work in our laboratory has been directed towards establishing which fats or glycerides are thrombogenic in the rat. Previously it was found that butter, together with agents which cause hypercholesterolæmia, such as cholesterol, cholic acid, and thiouracil,[6] produced thrombosis in the cardiac chambers, aorta, and coronary arteries, and also myocardial infarction. If butter was replaced by arachis oil no thrombosis or infarction occurred, but atherosclerosis of the proximal aorta and coronary arteries was produced. Butter differs from arachis oil in having a high content of saturated fatty acids and a low content of the diunsaturated linoleic acid. Groups of rats were given the above-mentioned diet, containing 40% fat, 5% cholesterol, 2% cholic acid, and 0·3% thiouracil, throughout life. Butter, beef fat, and hydrogenated arachis oil, which consist chiefly of saturated fatty acids linked to oleic acid, produced thrombosis but no atherosclerosis. Two synthetic glycerides, containing the saturated fatty acids mono-oleo-

1. Acheson, R. M. *Lancet*, 1960, ii, 706.
2. Wright, H. B. *ibid.* p. 980.
3. Gresham, G. A., Howard, A. N. *Brit. J. exp. Path.* 1960, **41**, 395.
4. Gresham, G. A., Howard, A. N. *Lancet*, 1960, ii, 527.
5. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., Wilcox, B. B. *Amer. Heart J.* 1948, **36**, 683.
6. Thomas, W. A., Hartroft, W. S. *Circulation*, 1959, **19**, 65.

distearin and dioleomonostearin, gave similar results; but triolein, containing only the monunsaturated acid, produced no lesions. It was therefore concluded that saturated fatty acids are essential for thrombosis. Arachis oil and maize oil, with a high content of linoleic acid, produced atherosclerosis. Linoleic acid given as trilinolein was ineffective, but a supplement of pure methyl linoleate added to butter gave atherosclerosis in addition to thrombosis. It would thus appear that linoleic acid required the presence of saturated fatty acids in order to exert an atherogenic effect. Further work with other synthetic glycerides containing linoleic acid is, however, necessary before this point can be fully established. The glycerides concerned in thrombosis and atherogenesis may function independently since both thrombotic and atherosclerotic lesions occurred with butter and arachis oil mixed in equal proportions.

This and other experimental methods of approach to the problem of atherosclerosis are valuable mainly because it is impossible to recognise the presence of atherosclerosis or thrombosis in man during life. The disorders are, most likely, due to various factors of which diet is only one. Nevertheless it is important to test each factor in the experimental animal. In the case of diet an excess of the agents tested must be used if any result is to be obtained in the absence of other predisposing causes. This method, which has always provoked criticism,[7] may provide valuable leads to further experimentation. Thus as a sequel to our work with rats, we have demonstrated that similar fibrous plaques can be produced in rabbits—a more susceptible species—by giving a synthetic diet containing 10% fat, and without cholesterol or other hypercholesterolæmic agents.[8] The role of dietary fat in this case, however, is rather obscure. Rabbits given beef fat, butter, and corn oil all developed such lesions, whereas none was seen in rabbits given a commercial pellet diet.

The stimulus for this experimental work which we report is derived from a careful detailed study of human disease in the post-mortem room. In our case there is no difference of opinion between laboratory worker and theorist, as suggested by Prior.[9]

Department of Pathology,
University of Cambridge.

A. N. HOWARD*
G. A. GRESHAM.

DICHLORPHENAMIDE FOR RESPIRATORY INSUFFICIENCY

SIR,—Dr. Simpson (Jan. 7) rightly points out the difficulty of assessing any drug in emphysema. I agree that patients with an arterial pCO_2 persistently above 55 mm. Hg are uncommon; and therefore report my experience with dichlorphenamide which differs from his.

4 patients with pCO_2 consistently greater than 60 mm. Hg were given dichlorphenamide 50 mg. four times daily for 4 weeks. In 3, pCO_2 was not reduced; in the 4th it fell from 63 to 47 mm. Hg, but three days later reverted to 63 mm. Hg when the patient developed an exacerbation of his bronchitis while still taking the drug. 2 of these patients had right ventricular failure, but this had already responded to chlorothiazide, and the effect of dichlorphenamide could not be assessed. 3 patients noted the subjective improvement mentioned by Dr. Simpson; but none of the 4 complained of headache or nausea.

The disappointing feature of this drug is its apparent ineffectiveness in acute respiratory insufficiency. Thus in 3 further patients, treatment with dichlorphenamide, antibiotics, antispasmodics, and respiratory stimulants did not lower the pCO_2 and tracheostomy became necessary. In 2 patients the pCO_2 was lowered to normal limits by artificial ventilation; but in the 3rd aspiration alone (dichlorphenamide having been discontinued) reduced the pCO_2 from 59 to 45 mm. Hg.

I shall continue to use dichlorphenamide while experience is accumulating; but I wonder just what is gained by lowering pCO_2 by 5 (or even 15) mm. Hg?

Aintree Hospital,
Liverpool.

L. H. HARRIS.

MERCURY RESISTANCE AND EPIDEMIC STRAINS OF STAPHYLOCOCCUS AUREUS

SIR,—Observations made here indicate that the work of Dr. Moore [1] on a selective medium for epidemic phage-type staphylococci may have even wider clinical applications.

The umbilical stumps of neonates treated with mercurochrome provided profuse cultures of phage-type 80/81 staphylococci; and facial abrasions treated with the same substance frequently became infected with the same organism. This is not remarkable since kapok pillows frequently harbour pathogenic staphylococci.

A surgical colleague has commented upon the widespread sepsis which develops when mercuric chloride is used for irrigations after radical mastectomy. It would appear wise to discontinue administering such mercurials to deal with stray malignant cells after abdominoperineal resection of the rectum.

In-vitro experiments have shown that the concentrations of mercurochrome and red mercuric iodide in which phage-type 80/81 can proliferate are low (e.g., 1 in 10,000 and 1 in 19,000 respectively), but these critical dilutions are quite conceivably reached in some areas by mixture with tissue-fluids. So far thiomersal ('Merthiolate') has been diluted down to 1 in 147,000 without staphylococci proliferating.

By employing mercurials which inhibit weak or non-pathogens, the formation of antibacterial substances inhibiting growth of epidemic phage-type staphylococci is prevented. The latter can then proliferate freely; this may well prove disastrous in wound, obstetric, and burn cross-infections.

Only antiseptic solutions with demonstrably effective lethal action in high dilution against the epidemic phage-type staphylococci should be used.

National Health Institute,
Wellington,
New Zealand.

H. T. KNIGHTS.

SIR,—After you published the interesting paper by Dr. Moore,[1] we endeavoured to confirm his results.

218 strains of *Staphylococcus aureus* isolated from routine bacteriological specimens were phage-typed and tested for mercury resistance in the way he described. We analysed our results to show the association between the phage-types and mercury resistance, using Yule's coefficient of association. The results, shown in the accompanying table, are quantitatively similar to Dr. Moore's.

Association between phage susceptibility and mercury resistance

Phage	*No.*	*Coefficient of association and standard error*	
80	49	+0·72	±0·08
83A	45	+0·69	±0·12
52	35	+0·58	±0·13
6	14	+0·43	±0·23
81	18	+0·49	±0·21
77	20	+0·39	±0·22
52A	40	+0·34	±0·16
47	30	+0·32	±0·18
54	21	+0·26	±0·22
53	25	+0·18	±0·21
75	16	+0·17	±0·25
7	15	−0·39	±0·28
55	16	−1·00	...
71	19	−1·00	...
79	35	−1·00	...

3A, 3B, 3C, 42E, and 42D, 29 and 187; all less than 10 strains each.

In our material 3 phage-types never showed mercury resistance. While certain strains such as 52/52A/80 or 83A were invariably mercury-resistant when alone, when combined with type 79 they were invariably sensitive. In addition, we studied the association between mercury resistance and penicillin resistance. The association is highly significant ($\chi^2=44$;

7. Gordon, I. *Lancet*, 1960, ii, 602.
8. Gresham, G. A., Howard, A. N. (1961). To be published.
9. Prior, A. P. *Lancet*, 1960, ii, 817.

*Member of External Scientific Staff of the Medical Research Council.

1. Moore, B. *Lancet*, 1960, ii, 453.

$P < 0.1\%$, $Q = +0.89 \pm 0.06$). If the untypable strains are excluded, all the mercury-resistant strains are penicillin-resistant.

We should like to thank Dr. J. O. Pryce for the statistical analysis.

R. J. LEEMING
M. A. BUTCHER
M. J. MEYNELL.

The General Hospital, Birmingham.

PROPRIETARY NAMES OF DRUGS

SIR,—Professor Wade's protest (Jan. 21) against the multiplication of proprietary names for the same product marketed in different countries emphasises the chaos that is developing in this field, to the increasing confusion of the medical and pharmaceutical professions.

But nothing can be more absurd than the policy now introduced by Messrs. Searle, who are currently promoting norethynodrel under the name of 'Conovid' as an agent for "fertility control". This firm already markets and advertises norethynodrel as 'Enavid', advocating its use for functional uterine bleeding. Conovid has the same composition as enavid but is marketed in 5 mg. instead of 10 mg. tablets. The justification given for marketing a separate pack under a different name is "in order to identify it specifically with fertility control and for the convenience of the Medical Profession when prescribing it for this purpose".

There can be no justification whatsoever for this policy. All drugs can be described and prescribed by their official or approved names, in an appropriate dose, and for a single firm to multiply its own proprietary names according to the therapeutic applications, or dose strength, of that product, is ludicrous. The physician or practitioner knows or should know the actions of and indications for the use of the drug, and it is a presumption to impose upon him separate trade-names. The further development of this policy might lead to a manufacturer marketing an antihistamine drug as 'Placiderm' for giant urticaria, as 'Placitrem' for parkinsonism, and as 'Placimer' for sea-sickness.

I do not wish to comment upon the merits of the preparation, or the ethics of its use. It is, however, unfortunate that the firm should have chosen to change the nomenclature of this particular drug, as this is a field where it is highly desirable that there be no confusion.

University of Aberdeen, Department of Materia Medica and Therapeutics. ALASTAIR G. MACGREGOR.

BROMELAIN AND THE CERVIX UTERI

SIR,—We were interested to read the paper by Dr. Duncan, Dr. Lawrie, and Dr. MacLennan.[1] Several points, however, deserve comment.

(1) In discussing the proteolytic and so-called mucolytic action of bromelain and other proteolytic enzymes, they state that hyaluronic acid is an important constituent of mucus. They imply that hyaluronic acid is also an important constituent of cervical mucus. We commonly find this misconception; it ought to be dispelled. Cervical mucus does not contain uronic acid,[2] nor is it affected by the enzyme hyaluronidase. These factors preclude the presence of either hyaluronic acid or the chondroitin sulphates. It has been suggested [3] that a sulphated mucopolysaccharide, containing equimolar amounts of glucosamine and galactose, is the functional entity. Others feel that the active material is a mucoid, that is, a glycoprotein rich in carbohydrate.[4 5] In mucoids the polysaccharide units (whether large or small) are strongly bound to a polypeptide chain. In our opinion it is confusing and premature to equate the term mucopolysaccharide with the unknown polysaccharide units that are tightly bound in the mucoid molecule.

(2) We now believe that the main constituent of the human and bovine cervical mucus is probably a mucoid and not a mucopolysaccharide. Electrophoretic separations of cervical-mucus proteins have shown that about 45% of the total protein is associated with a non-migrating and carbohydrate-rich fraction.[6] The action of trypsin and chymotrypsin eliminates the non-migrating fraction as well as the typical physical properties of the mucus such as *spinnbarkeit* and viscosity.

It is our opinion that the so-called mucolytic action of proteolytic enzymes on cervical mucus is nothing more than the hydrolysis of peptide bonds in the mucoid molecule.

Department of Obstetrics and Gynæcology, and Department of Physiological Chemistry, Wayne State University College of Medicine, Detroit, Michigan. KAMRAN MOGHISSI
OTTO W. NEUHAUS.

DIET RICH IN UNSATURATED FAT

SIR,—Having lived on a diet low in animal fat for the past year, I should like to comment on last week's paper by Dr. Lloyd and Miss Jukes.

The "milk" is expensive. In the evaporated form it is palatable but has to be diluted; in the dried form it is unpleasant whether in tea or coffee or to put on cereals, and it has to be reconstituted. It is much easier and cheaper to use separated milk in place of ordinary milk and take corn-oil in various ways.

The simplest way is as a salad oil or dressing but I also make cream. Equal quantities of corn-oil and separated milk, previously mixed in a bowl, neither heated nor sweetened, when pushed through a cream-making machine make a very palatable cream to take with fruit or cereals.

It should be mentioned that there are, of course, several brands of corn-oil in addition to 'Alfonal'. Some for sale in bulk are cheaper. The "margarine" is vitaminised, but I always think the oil should be.

London, N.8. STEPHEN COATES.

SKELETAL FLUOROSIS

SIR,—The findings of Prof. Amarjit Singh and his colleagues (Jan. 28) in the Punjab, India, may be considered together with some very similar observations on bones of villagers across the border in West Pakistan described by Kemp and Wilson in 1956.[7] The fluorine in the well-waters was derived from the older Aravalli rocks from the buried range which in certain areas cause shallowing of the alluvium of the Indo-Gangetic plain.

The storage of fluorine in bone is seen typically among less privileged peoples; but similar lesions may be determined by congenital or acquired renal disease in any population. In these cases the intake of fluorine in drinking-water is not necessarily high. This is of interest in Britain in view of the suggested extension of the mining of iron ores naturally rich in fluorine.

Oxford. DAGMAR C. WILSON.

SIR,—The advocates of fluoridation of water intended for public consumption would do well to consider very carefully the observations of Prof. Amarjit Singh and his colleagues (Jan. 28).

The fact that in 25% of the 46 cases showing obvious clinical signs of serious fluoride intoxication there was no evidence of dental mottling, even though the fluorine content of the drinking water was as much as 14 parts per million, is a serious blow to those amongst us who advocate the addition of this agent to water-supplies. Dental fluorosis is generally

1. Duncan, S. L. B., Lawrie, J. H., MacLennan, H. R. *Lancet*, 1960, ii, 1420.
2. Shettles, L. B. *Fertil. and Steril.* 1951, **2**, 361.
3. Zachariae, F. *Acta obstet. gynec. scand.* 1959, **38**, suppl. **1**, 86.
4. Werner, I. *ibid.* p. 39.
5. Gibbons, R. A. *Biochem. J.* 1959, **73**, 217.
6. Moghissi, K., Neuhaus, O. W., Stevenson, C. S. *J. clin. Invest.* 1960, **39**, 1358.
7. Kemp, F. H., Wilson, D. C. *Brit. med. J.* 1956, i, 1108.

recognised as a good indicator of cumulative fluoride intoxication; yet if it does not occur in such a high percentage of cases showing serious skeletal fluorosis it is illogical to assume that it is safe to medicate water for human consumption even if the level be kept below the proposed permitted maximum of 1 part per million (which can result in objectionable mottling [1]).

Institute of Pathology,
The Royal Infirmary,
Cardiff.

R. A. HOLMAN.

FIBRINOLYSIN AND HYALINE-MEMBRANE DISEASE

SIR,—There has recently been wide interest in the use of intravenous fibrinolytic agents.[2–5] A fibrinolytic drug for intravenous use has become available commercially in North America.[6] This "fibrinolysin"* is prepared from the globulin fraction of human blood-plasma, which contains the inactive precursor profibrinolysin. The precursor is transformed to active fibrinolytic material (plasmin) by a small amount of streptokinase and then it is purified.[5] According to Moser,[7] fibrinolysin has a preferential action on fibrin and attacks other plasma-proteins to a lesser extent. In humans, fibrinolysin has been reported to "consistently produce a significant degree of fibrinolytic activity in the circulating plasma", this activity being related to the dose given.[7]

Lieberman [8] has indicated that a deficiency of lung fibrinolytic activity may be of ætiological importance in the production of a hyaline membrane in the "respiratory distress syndrome". Gitlin and Craig [9] had previously proved that the membrane was largely composed of fibrin. These two observations inevitably lead one to speculate that fibrinolysin might find a place in the treatment of "hyaline membrane". Trials are now in progress to determine the effect of "fibrinolysin" intravenously or by aerosol inhalation on the prevention or resolution of hyaline membranes in the newborn.[10]

We have recently been investigating the action of fibrinolysin on fibrin clots in vitro. The clots were prepared from bovine fibrinogen (Armour) and topical thrombin (Parke Davis). The lytic activity was followed by measuring the decrease in opacity of the clot on a Klett photometer. Typical results are shown in the accompanying figures.

The opacity rises rapidly to a maximum in three minutes, remains constant for a time, and then gradually falls with increasing rapidity until lysis is nearly complete. The maximum opacity depends on the concentrations of fibrinogen and thrombin, on the molarity of the buffer, and on pH. The length of the lag period and the subsequent period of decrease in opacity (lysis) is dependent on the amount of "fibrinolysin" present, other factors being kept constant, but we were unable to establish a definite mathematical relationship between the amount of lysis and the amount of fibrinolysin at any point on the reaction curve.

Plasmin is heat-labile [11] and we have found that diminution of lytic activity can be readily detected if fibrinolysin is incubated at 37°C for 30 minutes and that the activity is almost abolished after incubation at 37°C for 6 hours. It seems remarkable to us that published methods for the estimation of lytic activity often recommend incubation at 37°C for some hours.

During the experiments it was observed that delay in the addition of thrombin to a mixture of fibrinogen and fibrinolysin resulted in a decrease in the maximum opacity of the clot and a prolongation of the time required for its development. Further investigation showed that fibrinogen which had been incubated at 37°C with fibrinolysin for 8 hours would no longer clot upon the addition of thrombin. Chromatograms of the fluid obtained after complete lysis of a fibrin clot by "fibrinolysin" revealed several ninhydrin-reacting spots which were absent from chromatograms of fibrinogen, fibrinolysin, or thrombin alone, but which were similar to chromatograms obtained from a fibrinogen-fibrinolysin mixture which had been incubated for 8 hours. It is concluded that fibrinolysin is not specific for fibrin, but that it has a considerable action on fibrinogen. This lack of specificity together with inactivation at body-temperature suggests that large and frequent doses would be necessary to maintain an effective plasma fibrinolytic level.

We believe these results are of some clinical importance if the in-vivo behaviour of fibrinolysin follows its in-vitro action. Fibrinolysin given intravenously to a baby developing hyaline membrane, might so alter the plasma-fibrinogen as to render it incapable of clotting. Such an effect could, theoretically, be dangerous if clot formation to prevent blood-loss became necessary. On the other hand, it could be beneficial if it would prevent the formation of a hyaline membrane. In babies who have already developed hyaline membranes, fibrinolysin could, in theory, act on the fibrin component of the membrane and lyse it. In our experience an amount of fibrinolysin which would lyse a clot completely if it were intimately mixed throughout the clot had very little effect if placed as a layer on top of a similar preformed clot.

It should perhaps be emphasized that our experience with fibrinolysin has been limited to in-vitro tests; its behaviour in vivo may be quite different. We have not attempted to assess the clinical value of fibrinolysin, but we think that much further investigation is needed before fibrinolytic agents can be recommended for treatment of hyaline membrane disease. From present knowledge it seems that this can be done only on the basis of properly controlled clinical trials. In our opinion a better method of assay of fibrinolytic activity is needed and this will require a better understanding of the underlying chemistry of fibrinolysis.

Department of Pædiatrics,
University of Alberta,
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E. J. TURNER
ALLAN G. STEWART.

1. Galagan, D. J., Lamson, G. G., Jr. *Publ. Hlth Rep., Wash.* 1953, **68**, 497.
2. Singher, H. O., Chapple, R. V. *Clin. Med.* 1959, **6**, 439.
3. Chapple, R. V., Singher, H. O. Reprint associated with a scientific exhibit, 108th Annual Meeting, American Medical Association, San Francisco, June 8–12, 1959.
4. Sussman, B. J., Fitch, T. S. P. *J. Amer. med. Ass.* 1858, **167**, 1705.
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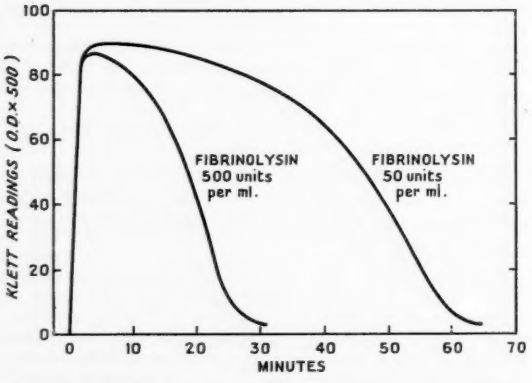
6. Information on 'Actase' (Fibrinolysin Human) supplied by Ortho Pharmaceutical (Canada) Ltd., Toronto.
7. Moser, K. M. *J. Amer. med. Ass.* 1958, **167**, 1695.
8. Lieberman, J. *New Engl. J. Med.* 1959, **260**, 619.
9. Gitlin, D., Craig, J. M. *Pediatrics*, 1956, **17**, 64.
10. Cornett, J. W. D. Personal communication.

* Fibrinolysin is used here to mean the commercial preparation called 'Actase' (Ortho Pharmaceutical Co.) available as a dried powder in vials of 50,000 units.



Influence of fibrinolysin on fibrin clots. Incubation mixture: fibrinogen (0·1%) 1 ml., fibrinolysin 0·5 ml., thrombin (5 units per ml.) 0·5 ml.

11. Fearnley, G. R., Revill, R., Tweed, J. M. *Clin. Sci.* 1952, **11**, 309.

REPRINTS

SIR,—Dr. Fauld's experience (Feb. 11) is not unique: one suspects a lucrative black-market for British reprints in the lower reaches of transatlantic academic circles.

I have never requested a reprint except by letter, nor willingly sent one—although this rigid approach has on occasions been modified when some postscript or other enlightened comment has indicated that the sender has read more than the title or the summary.

The reprint card—British, American, or Central European—is a phenomenon, cunningly designed by size and consistency to preclude obvious usage, and comparable only to the voluminous literature from drug houses. It is best ignored, but can give pleasure to small boys who collect foreign stamps.

Incidentally, the French never seem to send them: surely a proof that they are indeed the most civilised Europeans?

Department of Pathology,
Preston Hall Chest Hospital,
near Maidstone, Kent. P. FARNAN.

SIR,—Reprint collectors who order their supplies by printed postcards are, as Dr. Faulds observes, sometimes lacking in courtesy. One such request which made a more favourable impression here came recently from a Swiss laboratory, in the following terms:

Honoratissime collega!
Pergratum mihi feceris, si exemplar separate editum libri tui, qui inscribitur . . . mihi miseris.
Reverenter salutem tibi dicit!

To the less agreeable demands I have often thought of replying in their own idiom:

Dear Dr/Très honoré collègue/sehr geehrter Herr Kollege:
Nothing doing/Je ne marche pas/s geht nicht.

Regional Physics Department,
Western Regional
Hospital Board,
Glasgow. J. M. A. LENIHAN.

THE CIRCULATING CANCER CELL

SIR,—Your leading article [1] and the discussions on the work of Cole and his associates prompt me to recall some observations I made five years ago.

Impressed by the remarkable clinical properties of hypochlorite, I was studying the effects of exposing tissues and free cells, alive and dead, to the action of different concentrations of hypochlorite solutions. Using a phase-contrast microscope, I noticed that when 0·2% sodium hypochlorite was passed over an epithelial cell, the cell contracted rapidly to about half its size, and then within a few seconds began to swell. The cytoplasm liquefied and the cell membrane distended and ruptured within thirty seconds.

Of many solutions tested, only hypoiodite and hypobromite had the same effect; strong oxidising agents, varying strengths of chlorine water, and acids and alkalis were tried without result. The phenomenon seems to be a specific action of the halogen oxyacids, unaffected by the tonicity of the solution. No result was obtained if the concentration of the hypochlorite was below 0·18%.

The next step was to try hypochlorite on cancer cells. When live mouse ascites tumour cells were perfused the same phenomenon was seen—the cells immediately shrank and then swelled and burst, spilling their contents. But 0·5% sodium hypochlorite (as in Dakin's solution) proved to be unnecessarily strong. For any use that hypochlorite can be put to in surgery, a maximum concentration of 0·2% is adequate, and the clinical experience of many surgeons shows that, at this concentration, hypochlorite is for all practical purposes non-toxic. Though it will destroy free cells and necrotic tissue, the living cells in continuity with the tissues appear to be protected by a film of material formed by the interaction of hypochlorite and plasma, which is very resistant to further action of hypochlorite.

The American product, 'Clorpactin', referred to in your leader, has been recommended for use in cancer surgery. A recent paper by Atik et al.[2] has confirmed the experience of many workers that it is not effective in killing free cancer cells.

I reported this work at a meeting of the Medical Society of London three years ago. The film showing the action of hypochlorite on tissues and cells may be seen on application to me at 22, Seymour Street, Portman Square, London, W.1.

London, W.1. JOHN BUNYAN.

1. *Lancet*, 1960, ii, 476.

PSYCHIATRIC ASPECTS OF ACUTE PORPHYRIA

SIR,—I was interested to see from Dr. Myers' letter (Jan. 28) that at his hospital the Watson and Schwartz test [3] for porphyrins is now routinely performed on all patients admitted.

My interest in this subject was aroused by one of the cases which I reported in my letter of Jan. 14; we subsequently screened all the inpatients in this hospital, as well as all new admissions, by the same method. In just over a year, nearly 3000 urinalyses were carried out; so far not a single test has been positive for porphyrins. It will be interesting, as these surveys continue, to have a large number of estimations as a basis for reassessing the prevalence of this disorder.

Lancaster Moor Hospital,
Lancaster, Lancashire. M. D. CASHMAN.

BLOOD FIBRINOLYTIC ACTIVITY IN WHITE AND BANTU SUBJECTS

SIR,—Our previous studies on blood fibrinolytic activity,[4] using the clot-lysis technique of Bidwell [5] as described by Biggs and MacFarlane [6] and modified by Greig,[7] suggested that the blood fibrinolytic activity of Bantu subjects was greater than that of white subjects on identical diets. But the fibrinolytic activity of individuals tested on two separate occasions varied considerably, and while racial differences were significant in the first series of tests, in the second they were not. We could therefore not draw firm conclusions. We were not completely satisfied with the technique used, and have conducted further experiments using the technique of Fearnley et al.,[8] as modified by Lackner and Goosen,[9] with an automatic camera to measure the end-point of clot lysis. Our new results have differed similarly when the investigations were repeated on separate occasions.

Individuals on a constant diet who were tested on successive days after fasting overnight showed only slight variation in their blood fibrinolytic activity. But when the tests were repeated after 3- or 4-weekly intervals the variation was considerable. Ambulant white and Bantu subjects were tested on three separate occasions while on a "Bantu-type" diet, low in fat-calories, and high in fibre content. A small number of individuals were tested on only two occasions, and therefore in assessing the significance of changes on successive occasions only those individuals were considered who served as their own controls.

In the white subjects the mean clot-lysis times were $5{\cdot}8 \pm 3{\cdot}6$ hours, $8{\cdot}7 \pm 5{\cdot}0$ hours, and $7{\cdot}5 \pm 3{\cdot}4$ hours respectively. The difference between the first and second tests was highly significant ($P < 0{\cdot}001$); between the second and third not significant; but between the first and third still significant ($0{\cdot}02 < P < 0{\cdot}05$). For the Bantu subjects the corresponding times were $4{\cdot}7 \pm 3{\cdot}5$ hours, $5{\cdot}2 \pm 3{\cdot}4$ hours, and $6{\cdot}2 \pm 3{\cdot}3$ hours respectively. Here the difference between the first and second

2. Atik, M., Massari, F., Cohn, I. *Surg. Forum*, 1960, **11**, 76.
3. Watson, C. J., Schwartz, S. *Proc. Soc. exp. Biol., N.Y.* 1941, **47**, 393.
4. South African Institute for Medical Research. Report, 1959.
5. Bidwell, E. *Biochem. J.* 1953, **55**, 497.
6. Biggs, R., MacFarlane, R. G. Human Blood Coagulation and its Disorders. Oxford, 1953.
7. Greig, H. B. W. *Lancet*, 1956, ii, 16.
8. Fearnley, G. R., Balmforth, G., Fearnley, E. *Clin. Sci.* 1957, **16**, 645.
9. Lackner, H., Goosen, C. C. *Acta-hæmat.* 1959, **22**, 58.

tests was not significant; the difference between the second and third was highly significant ($P < 0.001$), and between the first and third was also highly significant ($0.01 < P < 0.001$). When means were compared by the "t" test, racial differences which were not significant on the first occasion were highly significant on the second occasion ($P < 0.001$), and were again insignificant on the third.

We have examined the frequency of the distribution of the activities within each racial group on each of the three occasions, and have found that for most volunteers the changes were minimal; but some individuals showed great variation when tested on successive occasions causing the mean for the group as a whole to change significantly. If the results from these individuals are excluded from the comparisons, then no significant racial differences appear to exist when fibrinolytic activity is measured by the above technique.

The reason for the variation in the results is not clear, and as extreme care was taken in the experimental technique, the recorded differences must either be inherent in the technique as a whole, or possibly be due to unknown variables in the methods of taking blood. Since these differences were highly significant, it is clear that no firm conclusions can be drawn in comparative fibrinolytic studies using the above technique. Published studies, using the above and the other techniques described in our previous report, have noted significant racial differences when the subjects were subsisting on their different natural diets. Most of these studies appear to have been carried out on single estimations of blood fibrinolytic activity, and the findings must thus be viewed with reserve until more precise methods are available for measuring blood fibrinolytic activity.

Ernest Oppenheimer Heart Research Unit, South African Institute for Medical Research, Johannesburg.

A. ANTONIS
I. BERSOHN.

LOCALISATION OF INGESTED TELEMETERING CAPSULES

SIR,—The superposition of the coils of the small intestine on the stomach and colon renders the localisation of telemetering capsules [1–3] difficult. Without knowledge of its position, the information which is transmitted by a capsule is of limited value, and to meet the problem we have devised an empirical method, using markers of contrast media.

One hour before taking the capsule the patient is given a small quantity of dilute barium sulphate or bismuth carbonate. A second marker is administered five hours later immediately before taking a radiograph. This outlines the stomach, and the first marker is usually found to be in the terminal ileum or proximal colon, with the capsule shown unambiguously between the zones—that is, in the small intestine.

A second radiograph is taken three or four hours later when the capsule would normally lie in the vicinity of the proximal colon, and a third after a further sixteen hours. Using the relative positioning of the capsule and the two markers in these radiographs, it is possible, in most cases, to interpolate, and thus to relate probable capsule position to the telemetered record. Abnormal delays or lack of progress along the alimentary tract are shown.

It is possible that the ingested marker substances could themselves have an effect on the motility of the gastrointestinal tract; this factor is being investigated. In the meantime this method seems to offer a solution until a non-radiographic method of location is obtained.

Medical Physics Unit, University of Edinburgh, and South Eastern Regional Hospital Board, Scotland.

MALCOLM RIDGWAY.

Department of Clinical Surgery, University of Edinburgh.

ADAM N. SMITH.

1. Jacobson, B., Mackay, R. S. *Lancet*, 1957, i, 1224.
2. Farrar, J. T., Bernstein, J. S. *Gastroenterology*, 1958, **35**, 603.
3. Connel, A. M., Rowlands, E. N. *Gut*, 1960, **1**, 266.

Q FEVER IN ARMY PERSONNEL

SIR,—The recent article by Surgeon Captain P. K. Fraser and his colleagues [1] prompts me to recount my experience of Q fever in the Army in Cyprus during 1957–59, when about 100 serologically confirmed cases were treated in the military hospitals in Nicosia and Dhekelia. The illness is intriguing, not only because it may easily be missed but also because it is often considered in terms of a "virus" pneumonia, the diagnosis of which still lacks precision because of the difficulty of identifying the ætiological agent, and the confusion over the clinical picture. That the disease is much more widespread than is supposed is confirmed by Fraser's article,[1] and MacCallum et al.[2] and Stoker [3] have written extensively on it. In England cases of Q fever seldom reach hospital, and are probably dismissed as pneumonia of uncertain ætiology, or "flu".

Epidemiology and Pathogenesis

Q fever in Cyprus, in 1957–59, occurred only between February and July, which represents the latter part of the wet season and the first half of the dry weather. Why infection should be confined to this period is not easy to understand.

In England rickettsiæ have been found in milk, which may transmit the infection, but in California dissemination by dust and inhalation of tick dejecta is thought to be a more probable portal of entry. In Cyprus, where the troops lived on tinned as opposed to fresh milk, the first source was eliminated, and, as in California, the respiratory tract was thought to be the route of infection. In Cyprus many sheep and goats, which abound with ticks, roam everywhere; the wind blows almost constantly later in the day and during the night, spreading dust everywhere, thus facilitating the spread of tick dejecta. One camp was rather more exposed than others, and it had the largest proportion of cases among its personnel. Insect bites were not conspicuous.

Signs and Symptoms

The onset of illness was fairly sudden, beginning with headache (of such severity that pethidine was sometimes necessary), associated with frequent vomiting and occasional meningismus, but lumbar puncture never revealed any abnormality. Anorexia was usually complete, and the tongue became covered with a greyish-white fur, but no rash was noted. Sweating was profuse, the temperature often reached 104°F, and the pulse was full and slow in proportion, varying little with the daily fluctuations in temperature of 3–4°F.

Examination of the chest often revealed no abnormality at first, and even after two days or more slight impairment to percussion, diminished air entry, and showers of fine sticky crepitations at the very end of inspiration were all that was to be heard. At no time were there pleurisy, tubular breathing, or rhonchi, and any of these signs would have obviated the diagnosis. Pre-existing pulmonary disease which might complicate the auscultatory findings were rare in these young men.

Cough may be absent, trivial, or appreciable. The sputum was invariably mucoid and often blood-streaked, or uncommonly it contained frank blood. Purulent sputum was not consistent with the diagnosis of Q fever.

The illness was usually over within seven days, and only once was this exceeded, this case lasting 5 weeks. Despite repeated X-rays no chest shadows could be demonstrated, although in the other series considered they were present in 90% of cases. Dyspnœa was not observed, neither was the spleen palpable.

Diagnosis

The complement-fixation test was performed on paired sera, the first taken between the fourth and eighth days of disease, and the second between the sixteenth and twenty-first. But if the second specimen of serum showed no rise in titre over

1. Fraser, P. K., Hatch, L. A., Carmichael, R. J., Evans, A. D. *Lancet*, 1960, ii, 971.
2. MacCallum, F. O., Marmion, B. P., Stoker, M. G. P. *ibid.* 1949, ii, 1026.
3. Stoker, M. G. P. *ibid.* 1949, i, 178.

the first, and the clinical evidence was strong, a third specimen taken seven to fourteen days later ofter resulted in a diagnostic rise. The highest titre recorded was 1/512 from the case where pyrexia lasted five weeks and in which no chest shadows were seen. This strongly suggests that lung involvement is only an incident, and that the lungs are not the chief site of infection.

Treatment

Because the disease seldom lasted more than seven days, and provided the patient was not distressed, tetracyclines were not usually given, but when these were necessary they seemed to influence the disease favourably.

Thus Q fever has distinctive clinical features, prominent among which are a high fever and relatively slow pulse, complete anorexia and heavily coated tongue, mucoid sputum, fine sticky crepitations heard at the very end of inspiration, and often ground-glass X-ray shadows which may be multiple, the illness lasting about seven days. Diagnosis is simply, and most easily, confirmed by complement-fixation tests on paired sera.

Military Hospital,
Colchester, Essex. H. FOSTER.

EFFECT OF IMMUNISATION WITH β-LIPOPROTEIN ON CHOLESTEROL ATHEROSCLEROSIS

SIR,—In a preliminary communication,[1] Gero et al. observed inhibition of atherogenesis by cross-species immunisation with β-lipoproteins.

Immunochemical methods had been used in our laboratory to investigate certain aspects of lipoprotein metabolism and the immunological properties of human β-lipoproteins[2]; and we applied similar methods to the study of experimental atherosclerosis and of the possible role of immunological processes in this condition. We felt it important and necessary first to repeat and extend the experiments of Gero et al. We produced atherosclerosis in rabbits and chickens by supplementing their diet with 1% cholesterol. The animals were bled 12 weeks later; and β-lipoproteins isolated from their blood were used for cross-immunisation in the other species. The immunisation was carried out for 6 weeks, half the animals receiving 1 intramuscular injection of the alum-precipitated antigen weekly (according to the schedule of Gero et al.), and the other half receiving 3 intravenous injections weekly.

The following groups of animals were used:

(1) Rabbits immunised with human β-lipoprotein, and then fed cholesterol.
(2) Rabbits immunised with chicken β-lipoprotein, and then fed cholesterol.
(3) Rabbits immunised with human albumin, and then fed cholesterol.
(4) Rabbits "immunised" with NaCl, and then fed cholesterol.
(5) Chickens immunised with rabbit β-lipoprotein, and then fed cholesterol.
(6) Chickens immunised with human β-lipoprotein, and then fed cholesterol.
(7) Chickens "immunised" with NaCl, and then fed cholesterol.

There were 10 animals in each group. Throughout the whole experiment, plasma total and free cholesterol and triglycerides were determined periodically.

The immunisation process itself did not affect the total and free cholesterol and triglyceride levels. In the chickens the average total cholesterol of the groups ranged from 140 to 180 mg. per 100 ml. before cholesterol feeding to 570 to 700 mg. per 100 ml. afterwards. The free cholesterol averaged 40 to 60 mg. per 100 ml. before and 400 to 480 mg. per 100 ml. after the cholesterol diet. The mean triglyceride level was 80 to 100 mg. per 100 ml. before treatment and 215 to 295 mg. per 100 ml. afterwards. All the groups, both immunised and control, fell within these limits and changed with the diet. In the rabbits the average pre-treatment level of cholesterol was 40 to 80 mg. per 100 ml. with post-treatment levels of 2150 to 2600 mg. per 100 ml. Free cholesterol levels at the end of the experiment ranged between 1400 and 1800 mg. per 100 ml. The mean triglyceride concentrations before treatment were 35 to 55 mg. per 100 ml., after treatment 70 to 135 mg. per 100 ml. All these values are group averages. Statistical analysis of the data failed to reveal significant differences between groups of immunised or non-immunised animals.

After four months of cholesterol-feeding all the animals were sacrificed and their vascular system was examined. All specimens were graded by two independent observers who knew only the code-number of the specimen and were therefore considered unbiased. In all groups of animals quite severe atherosclerosis developed and no difference could be found between immunised and non-immunised groups.

Similar conclusions were reported by Baker et al. in 2 recently published abstracts[3,4] using a somewhat differently designed experiment. We do not know why our findings failed to support Gero et al. Differences in the strain of rabbits or in the antigens that were used could conceivably be responsible for the discrepancies.

These investigations have been made with the support of the National Institute of Health, Bethesda, Maryland.

PETER E. SIEGLER
SUN J. RO
JOHN H. NODINE
Department of Medicine, Department of Physiology, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania. GEORGINA FALUDI-SIEGLER
JUDY A. SPITZER
JOHN J. SPITZER.

1. Gero, S., Gergely, J., Jakab, L., Szekely, J., Virag, S., Farkas, K., Czuppon, A. *Lancet*, 1959, ii, 6.
2. Spitzer, J. A. 21 Int. physiol. Congr. 1959, p. 262.
3. Baker, S. P., Markowitz, A. S., Szanto, P. B., Dubin, A. *J. Lab. clin. Med.* 1960, **56**, 788.
4. Baker, S. P., Markowitz, A. S., Szanto, P. B., Dubin, A. *Circulation*, 1960, **22**, 673.

TRISOMY IN MOTHER AND CHILD

SIR,—Mongolism in a woman, now aged 29, her daughter, aged 8, and her son, was reported by Hanhart.[5]

The son died, in 1956, at the age of 2 years. Dermal specimens from the woman, from her daughter, from her mother (aged 73), and from 2 brothers (of whom one is believed to be the father of her affected children), were sent to the Galton Laboratory for culture.

Preliminary cytological examination shows that the affected woman and the daughter each have 47 chromosomes, and appear to be of the standard mongol type.[6] The other three cultures contain cells with 46 chromosomes.

This seems to be the first full demonstration of secondary non-disjunction in man.

Zürich. E. HANHART.

JOY D. A. DELHANTY
Galton Laboratory, University College, London. L. S. PENROSE.

5. Hanhart, E. *Acta Genet. med., Roma*, 1960, **9**, 112.
6. Lejeune, J., Gantier, M., Turpin, R. *C. R. Acad. Sci., Paris*, 1959, **248**, 1721.

THE CASE AGAINST TRENDELENBURG'S POSITION

SIR,—The comments[7,8] on the Trendelenburg position prompt us to report our observations upon its effect on the blood-pressure after hæmorrhage.

In 5 dogs in a level supine position acute hæmorrhage was carried to the point of shock. After a period for stabilisation, the animals were placed in the Trendelenburg position, a position widely regarded in the United States as effective against shock. With the pressure transducer kept at right-atrial level, we found that the mean arterial blood-pressure consistently *dropped* by 5-10 mm. Hg. It might be asserted that cerebral blood-flow will be improved, in spite of a lower mean pressure, due to the hydrostatic advantage apparently enjoyed by the cerebrum in the Trendelenburg position. But the cerebral circulation is essentially a rigid U-tube, and the gravitational forces cancel out in such a system.[9]

7. *Lancet*, 1960, ii, 1183.
8. Kimbell, N., Loder, R. E., Richardson, H. S. *ibid.* p. 1354.
9. Rushmer, R. F., Beckman, E. L., Lee, D. *Amer. J. Physiol.* 1947, **151**, 355.

The theoretical advantage of increased venous return from the lower part of the body is obviously nullified by other factors. The slight decrease in arterial blood-pressure may be secondary to interference with the respiratory pump,[10] or due to the carotid baroreceptors "interpreting" the total intravascular pressure at that site as representative of the general *vis a tergo*.

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WARREN G. GUNTHEROTH
MÜFIT M. ARCASOY.

DIAGNOSIS OF ACUTE APPENDICITIS: THREE PHYSICAL SIGNS

SIR,—In the hope of making this diagnosis more certain, the three following physical signs are offered, because they have been found to be very reliable in practice. I have not found them described in textbooks or elsewhere, and they have proved valuable in cases of doubt.

Cæcal gurgling.—Sometimes palpation of the right iliac fossa leads to palpable gurgling of the underlying cæcum. When this is present it has been found that there has never been acute inflammation in the appendix. Acute appendicitis seems to be associated with conditions either in the cæcum itself, or in the overlying abdominal wall, preventing any gurgling in the cæcum.

Tenderness on movement.—In the case of children with suspected acute appendicitis it is helpful to stand them up and get them to "jump on the spot". If there is no increase in the pain in the right iliac fossa nor stabs of pain occurring at each jump, acute appendicitis is not present.

Stethoscope tenderness.—When a patient is examined for the first time, tenderness in the right iliac fossa is a frequent finding and not necessarily indicative of underlying inflammation. Even when all the usual measures are taken to relax the abdominal wall, such as bending the knees, warming the hands of the examiner, and feeling through a layer of clothing, tenderness may sometimes persist when there is no underlying organic cause. On such an occasion palpating the abdomen by means of pressing the bell of the stethoscope on the abdomen is often a help. Tenderness revealed by such a method is real tenderness, indicating inflammation. Another advantage of the method is that it enables any real tenderness present to be accurately localised. This sign is a great help in children and infants, particularly those who are crying when first seen.

Dudley Road Hospital,
Birmingham.

P. GILROY BEVAN.

PHENYTOIN IN THE TREATMENT OF TRIGEMINAL NEURALGIA

SIR,—The paper by Dr. Braham and Dr. Saia [11] is a welcome addition to the British literature on this subject, which has been well reviewed in Continental and American publications.

Credit is due to some earlier reports.[12–15] The use of phenytoin ('Epanutin', 'Dilantin', diphenylhydantoin) was pioneered in Germany by Albrecht and Krump [13] and Winiker-Blank,[12] and later in America by Ende [14] and King.[15] King also commented on the use of mephenesin alone and in combination with phenytoin. Ianone et al.[16] pointed out the latent period of 24–36 hours before the drug achieves its full therapeutic effect.

My experience of 9 cases of tic douloureux and 4 of postherpetic neuralgia dates from August, 1958, and parallels that of Braham and Saia.

Phenytoin in combination with phenobarbitone seems to increase drug toxicity with no increase in therapeutic effect. The dose may be at least double that suggested by Braham and Saia, with a corresponding increase in effect, which is particularly useful in bringing a bad attack under control. Continuous therapy for months on end is not necessary; treatment may be started by the patient if there are premonitory twinges of pain.

I associate myself strongly with the view of Braham and Saia that no patient should be submitted to radical treatment without an adequate trial of phenytoin.

With this first major advance in the drug therapy of tic douloureux it is to be hoped that alcohol injection and surgical extirpation of the trigeminal nerve will soon be eliminated.

London, S.E.10. HOWARD S. REEVE.

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RUPTURE OF THE INTERVENTRICULAR SEPTUM ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

SIR,—I read Dr. Schiller's paper [1] with interest.

We published a paper on the same subject some years ago.[2] One of our conclusions was that the systolic murmur pathognomonic of ruptured interventricular septum can be heard until the last moment of the patient's life, even when heart-sounds can no longer be discerned. Since then I have seen several more cases and confirmed this observation in all. This finding may be a diagnostic feature of rupture of the interventricular septum associated with acute myocardial infarction.

Department of Internal Medicine A,
Rambam Government Hospital,
Haifa, Israel.

HARRY BASSAN.

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2. Heichmann, Y., Bassan, H., Gellei, B. *Harefuah*, 1955, **49**, 160.

Parliament

Undermining or Underpinning?

ON Feb. 8 Mr. GEORGE BROWN moved a vote of censure deploring the proposed increases in N.H.S. charges and contribution because they indicated the Government's determination "to undermine the National Health Service and to place heavy burdens on those least able to bear them". Mr. Brown described the service as a noble edifice that needed a great and imaginative architect for its improvement and continuation. Instead we had a quantity surveyor. As a result we had descended from the real problems to fiddling about with quantities and bills of cost.

The Minister rested his case on the rising cost of the service. If it went higher, we should have to stop having desirable things. But Mr. Brown pointed out that at a round £860 million it was only a little over half what the nation spent on defence. Furthermore by itself a sum of money was no guide. It had to be looked at as a proportion of the national income, and, as a percentage of the national income, expenditure on the N.H.S. rested almost exactly where it was in 1950. In real terms, allowing for changes in the value of money, the expenditure in the service had only risen 2% a year since 1948. Was that too much for us? Was that a disaster? According to the figures for 1953 given in the I.L.O. report[3] we were only spending 4% of our national income in health. Even at that time only two developed countries (Holland and Denmark) were spending so little. Since then most other Continental countries had moved forward in their social services, but seven years later we were still spending only 4%, and when the next comparison was published it would look even worse. The Minister had also said that we could not have the new hospital building programme unless expenditure was curbed. But what did the programme, Mr. Brown asked, amount to? An increase of £5 million a year from now until 1965–66, yet the Minister proposed to take back through his charges and contribution £65 million a year.

The Minister had suggested that the increases were needed to curb waste—Mr. Brown presumed in the drug bill. But it was not the patient who was wasting money. We should have a full inquiry into the cost of drugs and the state of the pharmaceutical industry. Mr. Brown also deplored dearer welfare foods. They were preventive medicine and a really sensible method of avoiding waste. The extra prescription charge would

3. See *Lancet*, 1959, ii, 655.

fall especially heavily on those with chronic diseases and on those with small means and large families. The increase in the contribution was a £50 million poll tax imposed regardless of financial position.

Mr. ENOCH POWELL said that we were facing a period in which the hospital service, if it was to be modernised, would, in some respects, have to be radically altered. We could not have a modern hospital service unless the local health services were also expanded and modernised to give the hospitals proper support. This year the current expenditure on local-authority services was £100 million. Capital expenditure on these services had trebled in the last five years and this year was nearly £13 million (or about half the capital expenditure in the hospital service). He expected loan sanctions in the coming year to amount to £20 million. This capital investment programme was important, but even more so was the development of the right numbers and the right kind of personnel. The Government had already accepted the main recommendations of the Younghusband report, and he was glad to say that Sir John Wolfenden had agreed to become chairman of the linked national councils for the training of health visitors and social workers.

But the local-authority services could not be considered apart from the general practitioner service which had been substantially strengthened in the past five years by an increase of 5% in the number of practitioners and by a fall in the population in under-doctored areas from 21 million to 9 million. He was re-examining the data and calculations which underlay the estimate of the future of the size of the profession in the Willink report. In the past five years there had also been a 10% increase in the number of dentists working in the general dental service.

But these developments were inevitably reflected in the cost of the service.

The gross cost last year rose by 6%. It rose this year by 7% and next year it would rise by nearly 10%. The proportion of the gross national income which the service absorbed had increased over the last five years from 3·2% to 3·8% which was equal to the highest point at which it had ever stood, and it seemed clear that the proportion next year must be higher still. The net cost of the service to the Exchequer had increased by 6½% last year and by 8½% this year and, but for the Government's proposals, would increase next year by 11%. Even after the proposed changes, the net cost to the Exchequer will have increased over three years by about 20%.

A rate of increase in the cost to the Exchequer of that order could not continue; either the development of the service must be limited or its finances adjusted. There was a point beyond which the increasing cost could not be put on general taxation. In this situation the decision not to curtail the development of the service but to adjust its finances was taken, not to undermine the service, but to underpin it.

The proposed adjustment in N.H.S. finance had been criticised on the grounds that it placed heavy burdens on those least able to bear them. Mr. Powell agreed that the contribution fell irrespective of the earnings of the person by whom it was paid. There could be no mathematical standard of what was fair in such a relationship, but the contribution, as in 1946, was still just over 4% of the average male earnings. Again in 1946 it was decided that it would be fair for 21–22% of the cost of service to be borne by the contribution. Today, after the contribution was increased, only 16·7% would be borne by the contribution and even if all the charges were thrown in it would still only be about 21–22%.

Mr. Powell described the vitamin supplements as a "siege measure" introduced in time of war. An indiscriminate subsidy of this kind was no longer necessary. What we needed was something that would reach families in real need with the help of the local authority health visitor. The increases in charges for dentures and spectacles could not be said to represent a charge on the sick. He wished to emphasise that the prescription charge was not an alternative to other measures to limit the cost of the pharmaceutical services. The new voluntary price regulation scheme had opened the means of effective negotiation with the industry and other measures would be taken in coming months which would assist in economical prescribing within the general medical service and within the full professional discretion of the medical profession. Even of this charge it was not true to say, as a whole, that it was placed on the sick, because in many cases it would be paid by those who were earning, where the prescriptions were made out to dependants. Since 1952 when the 1*s.* charge was imposed, both benefits and wages had practically doubled. It was a ludicrous exaggeration to say that, by and large, the 2*s.* prescription charge was any more unfair than the 1*s.* charge in 1949. Where prescriptions were regularly needed doctors were not only able but were advised wherever possible to prescribe for two or three month's requirements. Where there was the possibility of genuine hardship, arrangements existed for the charges being refunded or for the money to pay for them being obtainable.

The motion was lost by 321 votes to 231.

The House then went into committee and Sir EDWARD BOYLE, the financial Secretary to the Treasury, moved the ways and means resolution of a Bill to give effect to the proposed increases in the National Health Service contributions. The liveliness of the discussion which followed later gave rise to difficulties, which were however of more political and procedural than medical interest.

On Feb. 9 Miss EDITH PITT, parliamentary secretary to the Ministry of Health, moved the second reading of a Bill to give effect to the proposed changes in charges for dentures and spectacle lenses and to give the Minister power in future to vary these charges by Statutory Instrument (a procedure that is already followed for other charges including prescriptions).

Mr. KENNETH ROBINSON asked if imposing charges was regarded as "underpinning the service", where would we stop? He deprecated the new powers given to the Minister in this Bill, for he feared that "vary" would prove a euphemism for "increase". After a debate the second reading was carried by 303 votes to 228.

On Feb. 13 Lord SILKIN introduced a motion condemning the proposed increase in the N.H.S. charges and contributions. In the course of the debate, in her maiden speech in the House of Lords, Baroness SUMMERSKILL stressed that hospital schemes could only be satisfactory if at the same time we improved the domiciliary services, and to put any barrier between the patient and the general practitioner diminished the therapeutic and preventive value of these services.

Medical Termination of Pregnancy Bill

On Feb. 10 Mr. KENNETH ROBINSON, in moving the second reading of his Bill,[1] said that its primary purpose was to put into statutory form what was now the established case law on abortion. It did not seek to legalise abortion but to allow doctors within certain defined limits, in certain circumstances, to exercise their medical judgment in good faith, unfettered by the threat, however remote, of criminal sanctions.

The present law and practice in this country could be described in two ways. One might charitably say it was the good old typical British compromise. Or one could also say, perhaps more accurately, that it was a rather unpleasant example of the hypnotic element which dominated the attitude to sexual matters in Victorian England. The statute law derived from the Offences Against the Person Act, 1861—which made it clear that it was a felony to administer drugs or to use instruments to procure an abortion. This Act placed that operation in a unique position. It was the only surgical operation which was interfered with by the law in any way. Sterilisation, both of the male and of the female, was regarded as a legal operation. Leucotomy which could change a patient's personality was legal.

The case law on abortion was a very different matter. For a long time it had been generally regarded as legal to terminate pregnancy to save the life of the mother. About 20 years ago, in Rex *v.* Bourne, that case law was extended to cover the mother's health as well as her life. He was told that it was

1. See *Lancet*, Feb. 4, 1961, p. 256.

improbable that the Bourne judgment would be overthrown by a higher court, but it did not carry anything like the force of statute law. This gave rise to an unsatisfactory situation. Some doctors took the view that all therapeutical abortions carried out in good faith were legal and they performed these operations openly in hospital on the basis of their medical judgment. Others were frankly frightened by the legal situation and preferred to have nothing whatever to do with it even though on their medical judgment alone in many cases they would either perform the operation or make arrangments for it to be performed. This meant that pregnant mothers were treated in a capricious sort of way according to who their general practitioner was, what town they lived in, and what hospital they were sent to.

Two consequences of great importance flowed from this. First, of course, was the flourishing trade of the so-called backstreet abortionists. He believed that some 50,000–100,000 of these unskilled operations were performed every year. The second consequence of the present state of the law was the existence of the skilled, fully qualified professional abortionist. Because of the possibly criminal aspect of the work they were able to demand large fees. It was a perfectly simple matter for anyone who had sufficient money to get a pregnancy terminated today by a qualified medical practitioner on the flimsiest of medical grounds. There was one law for the rich and one law for the poor. He did not suggest that the Bill would eliminate unskilled abortions, for the bulk of illegal abortions were probably carried out for reasons not included in the Bill. But some pregnant women had to go to illegal abortionists because their doctor was unwilling, in the present unsatisfactory state of law, to take a chance, even though his medical judgment indicated the pregnancy should be terminated. Surely it was infinitely better, whatever fraction of the total number of abortions this would represent, that they be performed by skilled doctors in the full light of day, preferably in hospital, with proper hygienic surroundings and as part of the National Health Service. If the Bill achieved no more than that it would still have been worth putting on the Statute Book.

Mr. PETER RAWLINSON opposed the Bill because he thought that as the law stood there should be no doubt about a doctor's duty. The law said that a doctor might lawfully terminate a pregnancy if, in his opinion, the mental or physical health of the mother-to-be would be seriously impaired. What more did society want? In Mr. Rawlinson's view, the Bill must widen and loosen the safeguards which a State or community was entitled to demand in the care which must be devoted to living but unborn children. Nor did he see how the termination of pregnancy could be a solution to some of the social problems and hard cases to which Mr. Robinson had referred.

Mr. DAVID RENTON, the under-secretary of State for the Home Department, said that the Government had no objection in principle to the Bill's limited purpose of putting into statutory form the present case law and practice. But the Bill also made important and controversial changes in the law, extending the opportunities for legal termination of pregnancy, and in doing so it gave rise to serious practical and legal difficulties. If the House gave the Bill a second reading, the Government hoped to see it amended in committee to eliminate or overcome some of these difficulties. For instance, in the view of the Ministry of Health, it was still not possible to predict with any confidence whether a child would exhibit some form of abnormality or how severe that abnormality would be. Where the transmission of abnormality was most probable and the degree of severity greatest it was the general experience that the state of mind of the expectant mother justified the termination of her pregnancy on the grounds of her health, and he did not believe, with the discretion which the present law allowed, that responsible doctors felt there was an unreasonable restriction. The relevant clause in the new Bill was drafted in such wide terms—and in the present state of medical knowledge it was difficult to see how this could be otherwise—as to permit of considerable abuse.

After further debate, although two attempts were made to move the closure, the Bill was talked out.

QUESTION TIME

Prescription Charges

Mr. G. THOMAS asked the Minister of Health what reduction in the number of prescriptions he expected as a result of the increased charge of 1*s.* per item.—Mr. ENOCH POWELL replied: My estimate will be based on a 2% reduction. Mr. THOMAS: Will the Minister be kind enough to tell me the number of prescriptions involved? It is obviously a very serious matter if people are not able to afford to pay for the prescriptions which their doctor thinks they ought to have. Could he tell me the number of prescriptions involved? Mr. POWELL: Not without notice. The principal factor in the reduction is the elimination of the prescriptions under 2*s.*

Refunding Prescription Charges

Mr. KENNETH ROBINSON asked the Minister of Pensions and National Insurance what was the current annual administrative cost of refunding prescription charges by the National Assistance Board.—Mr. J. A. BOYD-CARPENTER replied: About £145,000 a year, mainly costs incurred by the Post Office on behalf of the Board.

Hospital Accommodation and Convictions

Mr. KENNETH ROBINSON (by private notice) asked the Minister of Health why he was unable to provide hospital accommodation and treatment for Peter David Hastings, who was sentenced at Nottinghamshire quarter sessions last week to five years imprisonment despite a medical report stating he was mentally sick and despite the court's expressed willingness to make a hospital order under the Mental Health Act 1959, had accommodation been available.—Mr. ENOCH POWELL replied: I am inquiring into the circumstances in which the availability of suitable accommodation for this type of patient was not brought to the knowledge of the court.

Newspaper Articles on Drugs

Lord AMULREE asked H.M. Government whether their attention had been called to an article by Mr. Colin Wilson in the *Sunday Dispatch* for Jan. 15, 1961, called " My night with the Beatniks ", and whether the paragraphs relating to the drugs marijuana and ' Preludin ' were not an incitement to commit an offence.—Earl BATHURST replied: The question whether an offence has been committed is not for the Government to pronounce upon. In view of the noble Lord's question, the article has been referred to the Director of Public Prosecutions, who has expressed the opinion that it is insufficiently specific to provide evidence of the commission of the offence of incitement. Lord AMULREE: My Lords, I should like to thank the noble Earl for his reply, but do not the Government think it is a deplorable state of affairs that encouragement to people to take these noxious drugs should appear so easily in the public Press?

Students and their Parents

IN the answer to a question Sir DAVID ECCLES, the Minister of Education, said that under the present scale parental contributions in respect of grants to students were calculated at 14% of the balance of income in excess of £450 (£420 in Scotland). The revised scale, which will come into force on Oct. 1, required a contribution at the rate of 8% of the balance of income in excess of £600 up to £1400, no contributions being required from parents whose balance of income is less than £700. The additional contributions required from those whose balance of income exceeds £1400 will be £10 for each £100 above £1400. In assessing the balance of income, deductions would be made from gross income on present lines, but the maximum allowances for each dependent child other than the award-holder would be increased from £170 to £200 and the allowance for educational expenses for other dependent children from the present maximum of £180 to £200. The maximum grant of £50 per annum would normally be paid irrespective of parental income.

According to a table included in the parliamentary answer, parents with an only child at the university, who had a gross

income of £2000 and a balance of £1900 after deduction of such recognised expenses as life insurance and mortgage interest, would under the new scale contribute £114 instead of £203.

Performance of Transistor Hearing-aids

Mr. JULIAN SNOW asked the Minister whether he was aware that the new transistor hearing-set, which had many advantages over the older 'Medresco' model, was nevertheless much less powerful, was of little use to seriously deaf persons, and had no adjustment for pitch; and whether he would cause inquiries to be made with a view to rectifying these deficiencies.—Miss PITT replied: The medresco transistor-aid is not less powerful than the valve aid, but a still more powerful earphone is being developed for the profoundly deaf. The transistor-aid, however, has a different quality of tone, and this may be why some users find it less satisfactory. The possibility of modifying the tone is being investigated.

The Exchequer's Share

Since 1948 the percentage of gross National Health Service expenditure (excluding expenditure by, and grants to, local authorities) borne by the Exchequer has been:

	%		%
1948–49	74	1955–56	82
1949–50	79	1956–57	83
1950–51	84	1957–58	80
1951–52	83	1958–59	75
1952–53	82	1959–60	75
1953–54	81	1960–61 (latest estimate)	
1954–55	82		76

M.R.C. and Mental Health Research

Of the total funds available to the Medical Research Council over the past five years, the percentage spent on mental health research was:

	%		%
1956–57	2·3	1959–60	4·4
1957–58	1·8	1960–61	4·7
1958–59	3·8		

Shortage of Midwives

On the basis of deficiencies notified by hospital authorities, the shortage of midwives in the hospital service in England and Wales is about 700. Deficiencies in the domiciliary service notified by local health authorities total about 400. Understaffing occurs in many though not all areas, but follows no significant pattern.

Public Health

Diphtheria in London and Birmingham

Two outbreaks of diphtheria were reported last week. In London, children attending a training centre for the educationally subnormal in Wallingford Avenue, Kensington, were affected. This centre serves not only Kensington but also a number of other boroughs. 2 children have died (1 in Islington, and 1 in Paddington), 2 are confirmed cases, and 3 (1 each in Hammersmith, Islington, and St. Pancras) have been admitted to hospital as carriers. *Corynebacterium diphtheriæ gravis* has been isolated.

In Birmingham, all the cases so far have come from the Hockley district. A 6-year-old boy has died—the first diphtheria death in the city since 1955—and a girl of the same age is in hospital with the disease. 4 carriers (2 adults and 2 children) are also in hospital, and so, as a precautionary measure, are the dead boy's brother and sister.

Respiratory Infections

Deaths from influenza rose to 1219 in the week ended Feb. 4, compared with 699 the week before, and 36 in the corresponding week in 1960. 37 of the deaths took place in the administrative county of London.

Deaths from pneumonia in the same week exceeded 2000 for the first time this year. They totalled 2060, as against 1614 in the previous week, and 682 in the equivalent week in 1960. Influenza virus of variety A2 has again been isolated in many areas.

Obituary

MARY ADDAMS LESLIE-SMITH
M.B. Lond.

Dr. Leslie-Smith, who died on Feb. 3, served the New Sussex Hospital for Women, Brighton, as pathologist for almost thirty years, until her retirement in 1955.

She studied medicine at the London School of Medicine for Women and at St. Mary's Hospital and after graduating M.B. in 1923 she held appointments in the pathology departments of St. Mary's and of Ancoats Hospital, Manchester. Of her work at the New Sussex Hospital, S. I. writes: "Mrs. Leslie-Smith founded, staffed, and developed her department in the face of many difficulties, which a lesser character might have found insurmountable. This department gave unstinted service both in the hospital and in the town. Its reputation owed everything to her own vigour, ability, and enthusiasm. She cared profoundly for the welfare of people. She was always approachable, and never too much occupied to offer interest, help, and advice. Her later years were clouded by ill health and by family sadness, but she never ceased to give of her best. No hospital staff could have wished for a more delightful colleague. Her example and exertions are a part of our tradition, and she made her department a focal point in the life of the hospital."

Dr. KEITH THOMPSON

W. S. R. writes:

"When Dr. Keith Thompson came to the Queen's Hospital, Birmingham, I was amongst his first group of post-mortem clerks. That was nearly 30 years ago and it started an association which continued to his death. I saw him put new life into an old department, vividly teaching the principles of pathology in a manner which related them to life and not to death. He was a sportsman and he made one work. In all the years that followed he was instantly available, yet the busiest man of the lot. He has made a trip of over one hundred miles at a telephone request for help from a peripheral hospital far from his own group which was hamstrung with cross-infection. He has overcome uninformed obstruction and ignored insolent familiarity because as he said, 'They are not relevant to the problem.' The problem was always the centre of his activities and the motivation of his scientific life. He adopted other people's surgical problems. His wise, generous, and stimulating help will be missed in many places."

Appointments

ABBEY, PAUL, M.B. Lond., F.R.C.S., D.L.O.: part-time consultant E.N.T. surgeon, Southampton hospital group.

DAVIES, S. L., M.B. Wales, D.P.M.: senior assistant psychiatrist, Middlewood Hospital, Sheffield.

LIVINGSTONE, P. D., M.B. Edin., F.R.C.S.E.: consultant general surgeon, Rotherham area.

NICHOLSON, BASIL, M.B. Manc., D.T.M.&H., D.P.H.: senior M.O., duties mainly concerned with the school health service, Gloucestershire.

SCOTT, J. F., M.B. Dubl., D.P.M.: psychiatrist (S.H.M.O.), St. Ann's Hospital, Canford Cliffs, Bournemouth.

WIGFIELD, W. J., M.B. Cantab., D.P.H.: deputy M.O.H. and deputy principal school M.O., Eastbourne.

Liverpool Regional Hospital Board:

MIDDLEFELL, ROBERT, M.B. Lpool, D.P.M.: assistant psychiatrist, Deva Hospital, Chester.

OZORIO, H. P. L., M.B. Hong Kong, F.F.A.R.C.S., D.A., D.OBST.: consultant anæsthetist, St. Helens and Warrington areas.

SCOTT, D. L., M.R.C.S., F.F.A.R.C.S., D.A.: consultant anæsthetist, St. Helens and South Liverpool areas.

Western Regional Hospital Board, Scotland:

BREWIN, T. B., M.B. Lond., M.R.C.P., D.M.R.T.: consultant radiotherapist, Glasgow Royal Infirmary and associated hospitals.

FRAIN-BELL, LOCKHART, M.B. St. And., F.F.R., D.M.R.D.: consultant radiologist, Dumfries and Galloway Royal Infirmary.

GIBB, MURIEL E., M.B. St. And., D.L.O.: assistant E.N.T. surgeon, Ayrshire area.

STRANG, ROBERT, M.B. Glasg., F.R.C.S.E.: senior casualty officer, Stirling Royal Infirmary.

WOLFSON, Bernard, M.B. Glasg., F.F.A.R.C.S., D.A.: assistant anæsthetist, Western Infirmary, Glasgow.

Notes and News

A CENTRAL OFFICE FOR UNIVERSITY ADMISSIONS

SINCE 1958 an ad hoc committee of the Committee of Vice-Chancellors and Principals have been considering the procedure for the admission of students to universities. The ad hoc committee has already issued two reports in which it suggested simpler and more uniform methods of admission which have proved useful. In its third report [1] the committee says that it has been forced to the conclusion that the time has come when universities must consider the establishment of a central organisation and a central office to deal with applications for admission. Precise figures are not available, but it is generally agreed that not only has the number of candidates increased since 1955 but that on an average each candidate submits 3-4 applications as against slightly more than 2 in 1955. Thus in 1960 there were 151,000 applications for 22,650 admissions and if the number of applications continue to increase at the present rate, by 1964 it may exceed 200,000 even disregarding the peak of the " bulge " which should reach the universities about that time.

The report describes three schemes for setting up a central office. Both the schemes which the committee consider feasible provide for a central office equipped with data-processing machines, to which each candidate would make his application, naming a limited, but reasonably generous, number of institutions to which he wishes to apply. It would be the duty of the central office to distribute his applications to the institutions, to act as the channel through which all offers (firm or provisional) or rejections are conveyed to the candidate, to ensure that no other application remains in force once a candidate has firmly accepted a firm offer. The report deals with the universities of England and Wales, excluding Oxford and Cambridge, but the committee hopes that they too will consider joining the scheme, or at least help by completing their selections if possible by the end of December. Both the proposed schemes could include the Scottish universities, or it would be possible to set up a separate Scottish office.

SOUTH-EAST LONDON GENERAL PRACTITIONERS' CENTRE

LAST Thursday Lord Cohen of Birkenhead was to open the South East London General Practitioners' Centre at St. Mary's Road, Peckham. The centre will provide family doctors in the area with means of diagnosis and treatment which they do not have in their surgeries. It has an operation room where practitioners can perform minor surgery, a pathological laboratory, and X-ray, dark-, and viewing-rooms. Nursing staff will carry out treatment on the doctors' instructions, and there will be cooperation with health visitors and other social workers. There are two consulting-rooms and a common-room with books and other information, where conferences, film shows, and informal discussions can take place. The centre will be the first of its kind in the country to provide so wide a service to general practitioners. It is hoped, moreover, that it will also provide opportunities for medico-sociological research and, in collaboration with hospital medical schools, opportunities for undergraduate training in general practice.

The centre should stimulate and encourage the local practitioner and also provide a service which the patient will appreciate. The doctor will often be able to complete investigation and treatment which might otherwise have necessitated attendance at hospital.

The centre has been established by the London County Council with help from many sources. The Council has provided the premises (part of the former Pioneer Health Centre), adapted, furnished and partially equipped them, and will maintain them and supply nurses, health-visitors, and secretaries. The Nuffield Foundation has given a grant of £12,000, and the Sir Halley Stewart Trust has also given generously. The South East Metropolitan Regional Hospital Board and the Camberwell Hospital Management Committee have staffed and equipped the X-ray and pathological departments and are providing consultants.

The general management of the centre will be in the hands of a house committee, consisting of members of the L.C.C. and representatives of the general practitioners and of all the organisations concerned in the establishment of the centre, including the College of General Practitioners. The medical director of the centre is Brigadier H. L. Glyn Hughes.

1. Obtainable from 36, Gordon Square, London, W.C.1. (2*s.* 6*d.* post free).

WARD UNITS

THE third of the Ministry of Health's *Hospital Building Notes* [1] deals with the design of medical and surgical wards in non-teaching hospitals. It points out that the traditional open unit (reminiscent of Florence Nightingale and Scutari) is giving way to a multi-bed ward area subdivided by screens into bays of 4-6 beds. This concept allows the patients to be arranged in smaller groups, suitable to their nursing and social needs. But it may have to be modified in the light of current studies in cross-infection. An improved pattern of movement for nurses can be achieved by compact planning and the integration of ancillary facilities with bed areas. But it must be remembered that noisy areas such as sluice rooms and service lifts must be isolated from the patients' beds. The rearrangement of beds, so that they stand parallel to the window-wall, adds to the patients' comfort by removing glare. Not less than 20% of the beds should be available in single rooms for the isolation of patients with septic lesions. 27-32 beds is suggested as an appropriate size for a unit under the care of one ward sister. Plans for alternative layouts, and detailed descriptions of basic accommodation (including day and dining space) are included. Other sections give useful details about engineering services, including ventilation, heating and lighting, and telephones.

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Benzilonium Bromide	2-Benziloyloxy-1:1-diethylpyrrolidinium bromide Portyn
Cetoxime	*N*-Benzylanilinoacetamidoxime Febramine is the hydrochloride
Cyclopentolate	2-Dimethylaminoethyl α-1-hydroxycyclopentyl-α-phenylacetate Mydrilate
Epiœstriol	Oestra-1:3:5(10)-triene-3:16β:17β-triol 16-*epi*Oestriol Actriol
Erythromycin Estolate	Erythromycin propionyl ester lauryl sulphate Ilosone
Ethyl Dibunate	Ethyl 2:6-di-*tert*-butylnaphthalenesulphonate
Ethyloestrenol	17α-Ethyloestr-4-en-17β-ol
Fluphenazine	10-(3-[4-(2-Hydroxyethyl)-1-piperazinyl]propyl)-2-trifluoromethylphenothiazine Moditen is the dihydrochloride; Prolixin is the dihydrochloride
Isobuzole	5-*iso*Butyl-2-*p*-methoxybenzenesulphonamido-1:3:4-thiadiazole Stabinol
Methohexitone	α-(±)-5-Allyl-1-methyl-5-(1-methylpent-2-ynyl) barbituric acid Brevital; Brietal
Methoserpidine	10-Methoxydeserpidine Decaserpyl
Oxyphenbutazone	4-n-Butyl-2-*p*-hydroxyphenyl-1-phenyl-pyrazolidine-3:5-dione Tanderil
Phenampromide	*N*-(1-Methyl-2-piperidinoethyl) propionanilide
Prenylamine	*N*-(3:3-Diphenylpropyl)-α-methylphenethylamine Segontin
Prolintane	1-(α-*n*-Propylphenethyl) pyrrolidine 1-Phenyl-2-pyrrolidinopentane
Propiomazine	10-(2-Dimethylaminopropyl)-2-propionylphenothiazine Dorevane; Largon
Sodium Dibunate	Sodium 2:6-di-*tert*-butylnaphthalenesulphonate Becantyl
Sulphaurea	*p*-Aminobenzenesulphonylurea Euvernil
Tolpentamide	*N*-*cyclo*Pentyl-*N'*-toluene-*p*-sulphonylurea

Proprietary name	*Approved name*
Actriol	Epiœstriol
Becantyl	Sodium Dibunate
Brevital	Methohexitone
Brietal	Methohexitone
Decaserpyl	Methoserpidine
Dorevane	Propiomazine
Euvernil	Sulphaurea
Febramine	Cetoxime
Ilosone	Erythromycin Estolate
Largon	Propiomazine
Mydrilate	Cyclopentolate
Moditen	Fluphenazine
Portyn	Benzilonium Bromide
Prolixin	Fluphenazine
Segontin	Prenylamine
Stabinol	Isobuzole
Tanderil	Oxyphenbutazone

1. H.M. Stationery Office, 1961. Pp. 9. 1*s.* 6*d.*

SPRING SUPPLEMENTARY ESTIMATE

THE supplementary estimate[1] published on Feb. 7 includes £4½ million for the National Health Service in England and Wales. Additional sums are needed of £4½ million for the pharmaceutical services and £1½ million for the general dental services, but some of these can be found from appropriations already made.

ABSTRACTS OF HUMAN DEVELOPMENTAL BIOLOGY

A NEW abstracting journal, covering the experimental and clinical aspects of normal and pathological development in man, reproduction, transplantation, and some aspects of tumour formation, has been issued by the Excerpta Medica Foundation, aided by a grant from the Department of Health, Education, and Welfare of the U.S. Public Health Service. *Abstracts of Human Developmental Biology*,[2] which will be published monthly, will include approximately 2000 abstracts annually.

University of Glasgow

The Wellcome Trust has given a grant of £60,000 towards the cost of a new building for the department of genetics. It will be used to provide a suite of research rooms which will be named the Wellcome Laboratory.

On Feb. 4 the degree of M.D. was conferred *in absentia* on the following:

A. D. Hally (with honours); W. C. Watson (with commendation); W. F. D. Scotland.

University of Dublin

Mr. J. Seton Pringle, professor of surgery at the Royal College of Surgeons in Ireland, has been appointed regius professor of surgery in succession to Prof. A. A. McConnell, who is retiring.

Royal College of Surgeons of England

At a meeting of the council on Feb. 9 with Sir Stanford Cade, vice-president, in the chair, Sir Clement Price Thomas was appointed the Thomas Vicary lecturer for 1961. The Hallett prize was awarded to Captain W. E. Moffat, RAMC.

W. J. Dempster and O. D. Morris were elected to the fellowship *ad eundem*, and diplomas of fellowship were granted to R. C. F. Cilento and G. R. James.

Diplomas of fellowship in the Faculty of Anæsthetists were granted to the following:

P. M. E. Youngman, F. C. Shelley, P. H. Dennison, R. C. Nainby-Luxmore, Peter Brine, Betty V. Scott, Ruth R. Irvine, Mercedes D. Carvel, C. J. T. Archer, W. J. Hegarty, John Barker, W. J. Love, Margaret E. Burns, C. A. B. McLaren, A. I. Weinreich, Joan H. Breed, Mavis Buck, J. A. H. Davies, Hemanta Kumar Dutta, P. J. McQuade, W. D. A. Smith, Sukhdev Mehta, C. W. Thomson, R. D. Unkles, M. B. Yorston, R. S. J. Clarke, C. F. Conway, R. E. Davis, Patricia A. Edwards, Qamarul Haq, Latifi, J. A. Monro, Sandra Murdoch, E. F. Battersby, Sheena W. Campbell, H. J. L. Craig, J. G. Francis, E. G. Leonard, Robert Porteous, Miriam Stafford, D. A. C. Breslin, M. D. Churcher, J. I. Clayton, A. J. Clement, M. D. Hargreaves, M. E. Hayes, R. F. Knight, W. R. MacRae.

Licences to practise and diplomas were conferred, jointly with the Royal College of Physicians, on those mentioned in our issue of Feb. 4 (p. 291) and on the following:

D.L.O.—K. W. Murphy.
D.P.M.—H. C. Ferguson.
D.P.H.—M. B. Todd.
D.T.M. & H.—M. A. Mirza.

Royal College of Physicians of Ireland

At a meeting of the college held on Feb. 3, with Dr. R. E. Steen, the president, in the chair, the following were admitted to the licence and membership:

P. A. Browne, W. A. G. MacCallum, Edward Murphy, J. W. Nixon.

Mental Health Services

A conference on these services and the new Act is to be held by the Edinburgh and East of Scotland regional group of the Royal Institute of Public Administration from March 16 to 18 at Peebles. Further particulars may be had from the hon. secretary of the Edinburgh and East of Scotland regional group of the Institute, 20, Cockburn Street, Edinburgh, 1.

1. H.M. Stationery Office, 1961. Pp. 208. 11*s*. 6*d*.
2. *Abstracts of Human Developmental Biology*, vol. **1**, no. 1, January, 1961. Obtainable from the Excerpta Medica Foundation, 67, New Bond Street, London, W.1. £6 18*s*. per annum.

Royal College of Physicians of Edinburgh

At a meeting on Feb. 7 with Dr. J. D. S. Cameron, the president, in the chair, the following were elected to the membership:

C. D. Kennedy, R. O. Murray, T. A. Lambo, Julius Vahrman, Inder Dev Aggarwal, Coimbatore Subramania Rajagopal, Shyamal Kumar Sen, Hawa Patel, C. B. Macdonald, W. K. Cowan, H. C. White, Andrew Armstrong, S. H. Davies, Daniel Kelleher, Tin U, Gobinda Lal Chakrabarti, Nasnaranpattiyage Don Wilfred Lionel, Harold Jacobs, Mohammad Ashfaque Ahmad Khan, Chandra Madhab Chatterjee, Susan Kuruvilla, J. D. Fitzgerald, W. N. Morley, Shantakumar Dnyaneshwar Bhandarkar, Kankanamalage Dharmadasa, P. G. Livingstone, Sasanka Sekhar Ghatak, Susanta Kumar Datta, Dilip Kumar Datta, Kekobad Minocher Mody, Nazir Ahmad Chaudhary, Ma Khin Thaung Nyunt, Vijaya Chandra Ratnesar, Shirley G. Ratcliffe, J. P. A. McManus, F. R. Orr, Bruce Simpson, G. W. Friedland, Tantrimudalige Anthony Don Michael, Abdul Sattar Abbasi, I. M. Breckenridge, Om Parkash Bahl, C. H. Bastomsky, Louis Berman, Raymond Levy, Panini Ranjita Wikramanayake, Kamal Kumar Mallik.

British Congress of Obstetrics and Gynæcology

This congress will be held from July 16 to 18 in Bristol. Further particulars may be had from the hon. secretaries of the congress, University Department of Obstetrics, Southmead Hospital, Bristol.

Whole-time Consultants Association

The following officers have been elected:

President: Dr. A. A. Cunningham: hon. treasurer: Dr. R. M. Mayon-White; hon. secretary: Dr. J. Walter.

World Health Assembly

Opening the fourteenth World Health Assembly in New Delhi on Feb. 7, the Indian Prime Minister, Mr. Nehru, said that the World Health Organisation's work had been so successful because it had succeeded in avoiding the controversies and conflicts besetting other international organisations. He congratulated W.H.O. on its achievements in the Congo.

Sir Arcot Mudaliar, vice-chancellor of Madras University, was elected president of the Assembly.

Rockefeller Foundation

During the fourth quarter of 1960 the Foundation distributed $10,631,000. Grants for medical and natural sciences amounted to $3,115,000 and included a three-year grant of $20,000 to Strangeways Research Laboratory, Cambridge, for research in experimental biology, and a further grant of $23,000, to be spread over 2 years, to the South West Metropolitan Regional Hospital Board for research on the biochemistry of the nervous system, under the direction of Dr. Derek Richter at the M.R.C. neuropsychiatric research unit at Carshalton.

Medical Research Council

Fellowships in Clinical Research.—The Council invite applications for a further series of fellowships in clinical research, tenable at centres in the United Kingdom during 1961–62. These fellowships are open to suitably qualified medical graduates, who should preferably have worked for a period in a department in which clinical research was in progress. Further particulars and forms of application may be had from the secretary of the Council, 38, Old Queen Street, London, S.W.1, with whom applications must be lodged by March 23.

Hunterian Society

This society's annual dinner was held in London on Feb. 9, under the presidency of Dr. G. B. Mitchell-Heggs, who responded to a toast to The Society proposed by Sir William Dickson. Mr. D. C. Norris proposed The Lord Mayor and Corporation of the City of London, and Sir Bernard Waley-Cohen, the Lord Mayor, responded. Sir John Wolfenden replied for The Guests and Kindred Societies to a toast proposed by Dr. Oswald Savage.

Rehabilitation of the Amputee

A course for orthopædic consultants and senior registrars will be held from May 1 to 5 at the Limb Fitting Centre, Queen Mary's Hospital, Roehampton, London, S.W.15. Applications should be sent to the Principal Medical Officer, Artificial Limbs and Appliances (Med. 5 PL), at the same address.